

EXHIBIT 18

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON
(LHG)
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION

MDL NO. 16-2738 (FLW)

THIS DOCUMENT RELATES TO ALL CASES

RULE 26 EXPERT REPORT OF
SARAH E. KANE, MD

Date: November 15, 2018



Sarah E. Kane, MD

I. BACKGROUND:

I am certified by the American Board of Pathology in Anatomic Pathology, Clinical Pathology and Cytopathology. I received my medical degree from The Ohio State University College of Medicine in Columbus, Ohio. I completed my residency in Anatomic and Clinical Pathology at Massachusetts General Hospital, a Harvard Medical School teaching hospital in Boston, Massachusetts. Following my residency, I completed a two-year gynecologic and cytology fellowship as the Robert E. Scully Fellow in Pathology at Massachusetts General Hospital, named after Dr. Robert Scully, who was a giant in the field of gynecologic pathology. This fellowship was focused on gynecologic pathology, perinatal pathology, and cytopathology. I studied the causes and mechanisms of disease as part of my training, and studied gynecologic cancer and disease in depth during my fellowship training. To this day, I routinely follow the gynecologic pathology literature as part of my regular practice.

I am currently a full partner in a private practice group, Commonwealth Pathology Partners PC. I have staff privileges at Massachusetts General Hospital, North Shore Medical Center (consisting of Salem Hospital in Salem, MA and Union Hospital in Lynn, MA) and Newton-Wellesley Hospital. I was hired by Commonwealth Pathology Partners PC to be the group's gynecologic pathology expert. Although all of the anatomic pathologists in our group practice general anatomic pathology, our group employs fellowship-trained pathologists in many subspecialty areas of pathology. This means that I see the majority of gynecologic surgical pathology specimens from my hospital sites, and if another pathologist needs an opinion on a gynecologic case, I will review it. I also presently serve as the autopsy director at North Shore Medical Center. I regularly attend and participate in numerous multidisciplinary conferences at Massachusetts General Hospital at the Cancer Center site in Danvers, MA.

Before entering private practice, I was a staff pathologist and Instructor of Pathology at Beth Israel Deaconess Medical Center (BIDMC), another Harvard Medical School teaching hospital. During my time at BIDMC, I performed specialty sign-out in gynecologic pathology, perinatal pathology and cytology. I was also served as the Associate Director of the Cytopathology Fellowship Program at BIDMC, served on numerous pathology department committees, and taught several courses at Harvard Medical School before I was recruited for my current position. My curriculum vitae is attached as Exhibit A. It further details these positions and the remainder of my work experience in this field. Exhibit B details the references cited in this report, as well as other materials and data I considered.

I have been asked to provide an expert report regarding my opinions on the question of general causality in the case of talcum powder product use and ovarian cancer. All of my opinions stated below are held to a reasonable degree of medical and scientific certainty. I reserve the right to modify or change my opinion based on further documents or information that may be provided to me in the future.

A pathologist is a physician who has completed medical school and a post-graduate residency in pathology (either clinical pathology, anatomic pathology, or both). Like me, many pathologists go on to complete fellowships following their education and residency.

Pathology is the study of disease; pathologists spend much of their time both in training and in daily practice studying the causes and presentations of disease. The years of medical training are of critical importance in daily practice; pathologists must make clinical assessments, based in part on medical and epidemiologic knowledge, about identification of causes, risk factors, clinical sequelae, morphologic, and genetic features of disease.

In order to produce accurate diagnoses, pathologists must be knowledgeable about the medical, scientific, and epidemiologic evidence base. A knowledge of advancements in technologies applied to tissue samples must be continuously maintained. This involves not only maintaining current knowledge of the pathology literature, but also of the literature in various other fields such as oncology and other fields relevant to our practice.

One of the tools used in the process of identifying talc particles in tissue is polarized light microscopy. Anatomic pathologists routinely use polarized light microscopy in clinical practice. As an example, one might use polarized light microscopy to find foreign material and explain an inflammatory reaction. The most common application in my practice is for identifying calcium oxalate crystals in breast biopsies done for radiologically identified calcifications. I estimate I use polarized light microscopy for this purpose about twice a month.

In anatomic pathology, the pathologist not only needs to be aware of the numerous possible diagnoses, but also of the causes of diseases one may encounter in any given organ system. Coming to a diagnosis requires knowledge of the medical, scientific, and epidemiologic literature. Pathologists must be proficient in the current literature that informs and supports their conclusions.

Ultimately, a pathologist's diagnosis must make biological sense and must be supported by the weight of the available medical and scientific information. Not only must a particular case match the morphological characteristics of the diagnosis being made, but it must fit the clinical presentation, the patient history, and it must be consistent with what is known about the disease, including what is known about disease causation. These are the same medical and scientific information resources that I rely on for my opinions in this report.

Thus, the work that I've done in this report is similar to what I do in my daily practice. My clinical practice requires ongoing familiarity with the same medical evidence that I have considered here.

Ovarian cancer has an incidence rate of 11.8 per 100,000, and thus is relatively rare (Torre 2018). At my current private practice, I am the primary pathologist on approximately 6,000 cases annually. This includes both surgical pathology and cytopathology cases. I would be diagnosing, ruling out, or looking for ovarian cancer or metastatic ovarian cancer (among other diseases), in approximately 2000 cases a year as a rough estimate. Of those, I estimate that I diagnose about 30 cases per year as ovarian tumors. Academic teaching hospitals generally tend to have a higher volume of ovarian tumor cases due to their large referral bases. While I was a staff pathologist at Beth Israel Deaconess Medical Center, the pathology department implemented a subspecialty sign-out schedule in 2010. In my last two years there,

I signed out predominantly gynecologic surgical pathology in addition to cytopathology (in prior years the department had a general surgical pathology schedule, which meant all types of cases went to each anatomic pathologist regardless of subspecialty fellowship training). During that time, I estimate I signed out about 500 ovarian tumor cases per year. Similarly, while I was a fellow at Massachusetts General Hospital from 2005-2007, I independently signed out gynecologic surgical pathology and estimate I signed out approximately 500 ovarian tumor cases per year. As a resident in anatomic pathology at Massachusetts General Hospital, I was exposed to hundreds of ovarian tumor cases both during my clinical case work and didactic sessions.

Of note, during my time at Massachusetts General Hospital, both Drs. Robert Scully and Debra Bell were still working in the Department of Pathology. Dr. Scully was a co-author on Dr. Cramer's first paper on talc and ovarian cancer in 1982, and Dr. Bell was a co-author on Drs. Harlow and Cramer's 1992 paper on talc and ovarian cancer. Dr. Bell's tenure as Cytopathology Director also overlapped with my time there. This meant that I spent significant time with Dr. Bell during my residency and fellowship. I was the primary author of a paper on ovarian serous borderline tumors in 2006, with Dr. Bell serving as a co-author. Dr. Scully, known as a giant in gynecologic pathology, was semi-retired by the time I started my pathology residency in 2001. However, he was at the hospital nearly every day and all of the gynecologic pathologists would still show him cases on a consult basis. Dr. Robert Young, the director of my fellowship program, was a Scully protege and continued his consulting practice. It is because of my training at Massachusetts General Hospital and my interactions with both Drs. Scully and Bell that I first became aware of their work on talc and ovarian cancer. Since then, I have maintained a professional interest in and have continued to monitor developments in the science regarding talcum powder exposure and ovarian cancer, and it has been the subject of professional discussions pre-dating this litigation.

My billing rate is \$500 per hour. I have previously testified in one matter, a deposition for the case of Julie Lagadimas, as Personal Rep. of the Estate of Dawn M. O'Toole v. R.J. Reynolds Tobacco Co., et al; Norfolk Super. Ct. Case No. 1582-CV-01474.

II. GENERAL CAUSATION OPINIONS:

Based on assessing and weighing the totality of the evidence, and following the methodology set forth below, I hold the following opinions to a reasonable degree of scientific and medical certainty:

1. Talcum powder products and their constituent minerals can reach the ovaries through migration up the genital tract from the perineum to the fallopian tubes and ovaries. There is also evidence that these products can be transported through the lymphatic system (Cramer 2007). Another biologically plausible pathway is inhalation leading to lymphatic transport to the ovaries (Suzuki 1991, Marchiori 2010, Frank 2011).

2. Once reaching the ovaries, talcum powder products can cause chronic inflammation, can increase oxidative stress, and can reduce immune response. These are biologically plausible and likely mechanisms for ovarian cancer development and progression.

3. There are chemical similarities between asbestos and talc and there are striking pathological similarities between invasive serous ovarian cancer and mesothelioma.

4. There is evidence that talcum powder products manufactured by Johnson & Johnson (Johnson's Baby Powder and Shower to Shower) have contained and continue to contain asbestos, talc containing asbestiform fibers (fibrous talc), and heavy metals such as cobalt, nickel, and chromium. Other than cobalt, which has been identified as a "possible" carcinogen by the International Agency for Research on Cancer (IARC), all of these constituents have been identified as known carcinogens by IARC (IARC 1987, IARC 2012).

5. For purposes of my opinions, I have reviewed and relied upon Dr. Crowley's report regarding the fragrance chemical constituents in Johnson & Johnson talcum powder products (Crowley Report), as well as testing reports and analysis which include, Dr. Blount (Blount Report), Dr. Longo and Dr. Mark Rigler (Longo et al. Report), as well as the corporate testimonies of John Hopkins and Julie Pier. The presence of these constituents as part of talcum powder products provides additional evidence of biological plausibility for causation regarding talc and ovarian cancer.

My opinions and conclusions are supported by epidemiologic studies showing an increased risk of ovarian cancer in women who used talcum powder products for perineal dusting, animal and in vitro studies, cellular biology studies, and pathological evidence which provides a highly biologically plausible mechanism for talc's carcinogenicity. Based on the totality of evidence, it is my opinion to a reasonable degree of scientific and medical certainty, that perineal exposure to talcum powder products can cause epithelial ovarian cancer.

III. METHODOLOGY FOR ASSESSING CAUSATION AND PRINCIPLES OF CAUSAL INFERENCE:

For this report, I followed the same methodology that I use in my clinical practice and research, a method that is generally accepted in the medical community. I used the same standards for evaluating and interpreting medical and scientific evidence, and I followed generally accepted standards in science and medicine for assessing causation, including consideration of the Bradford Hill viewpoints.

My causal assessment in this case is based on my background, training, education and experience as a physician and pathologist in interpreting, comparing, and weighing the totality of the available biologic, pathologic and epidemiologic evidence. I considered this evidence in the context of the Bradford Hill causation assessment viewpoints to reach an opinion regarding whether talcum powder products¹ can cause epithelial ovarian cancer.

Bradford Hill's discussion of a causal relationship includes strength of association, consistency, coherence, specificity, temporality, biological plausibility, dose-response, experimental evidence, and analogy as different "viewpoints" of a causal relationship between

¹ In my report, the term "talc" is used to refer to talcum powder products.

an exposure and a disease. Consideration of Bradford Hill's approach to causation, which I discuss in more detail below, supports general causation of talcum powder product exposure and ovarian cancer. The Bradford Hill causation viewpoints are not a checklist of requirements, and it does not call for a mechanical application of his 9 considerations for assessing a causal relationship; rather, it is properly understood as providing a framework for an assessment of the totality of the evidence leading to a judgment about causation. As Bradford Hill himself put it, "What I do not believe...is that we can usefully lay down some hard-and-fast rule of evidence that must be obeyed....None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as the *sine qua non*." I agree with that statement.

My methodology began with a systematic review of the medical literature to ascertain the relevant body of scientific evidence that I would consider. This included consideration of a large number of peer-reviewed publications reporting the results of human epidemiological studies investigating the association between talc exposure and ovarian cancer. I also considered and weighed other lines of evidence pertaining to explaining relevant, plausible, and likely mechanisms for how talcum powder product exposure causes ovarian cancer. This included carcinogenicity studies and data regarding talc and its constituents. Counsel for plaintiffs also provided me with medical literature to review, most of which overlapped with materials that I found independently through my own medical literature searches.

Relevance is not simply a yes/no proposition; it is a variable that ranges from not relevant to directly relevant, and there is a range between these extremes. Only a careful review of the evidence leads to an assessment of the degree of relevance. Much of science involves extrapolation and generalization from one study to the general population. The assessment of relevance is based on the extent that the study results are pertinent to the issue under consideration.

Human data is generally more relevant than animal data when assessing causation in humans. However, animal studies on exposure and disease are performed to advance our understanding of the human response to the same dose-adjusted exposure, and thus animal data is often relevant and important in that it can provide important information that forms part of the total evidence assessment. For example, if an exposure to talc in a rat causes inflammation, that could be relevant to assessing the effect in humans.

All observational studies have limitations, requiring careful interpretation. Reliability determinations focus on the degree of confidence in a study's internal validity. Reliability, like relevance, is not a yes/no proposition. For human epidemiologic observational studies, reliability assessments entail consideration of alternative explanations, including the role of chance and the likelihood that the results are affected by bias or confounding. Factors to be considered include: (1) Do we have reliable and appropriate measures of exposure; (2) do we have reliable assessments of disease; (3) do we have comparable groups for comparison; (4) have the investigators adjusted for potential confounding; (5) are the study results likely the result of a systematic bias; and, (6) does the study have enough exposures and sufficient power to detect an association if it exists?

I also consider the type of study design and whether it is suited to the question being researched. There is a general hierarchy of evidence, which I also consider, but study type and its position in the hierarchy will only have value if the study is otherwise relevant and reliable. For example, a randomized clinical trial may be the “gold standard,” but one must still look at whether the study does in fact provide a relevant and reliable result for the issue of interest (here, whether talcum powder products are capable of causing ovarian cancer).

In weighing the evidence other important considerations include: How does the study define, ascertain, and measure talc exposure? What type of study was it? Other considerations include: Has the study been or can it be replicated? Is the study result consistent with other studies? Has the study been published and has it been peer reviewed? Has the study been conducted on a relevant population? How does the study adjust for potential confounders and how does the study minimize or account for bias? Is there a potential for misclassification of exposure or disease based on the circumstances under which the data was gathered or analyzed? What is the potential that study results could be due to chance, bias, or confounding? Is there a statistical analysis, with a reported error rate? Were the results statistically significant, and, if not, are the results still important when considered with all other evidence from the perspective of overall consistency? What is the size of the study population? Is the study large enough to detect an association if it exists? Do the results make biologic sense? This is a list of examples of considerations for weighing the evidence, and is not intended to be comprehensive.

In weighing the evidence, I also consider the reported “P values” and confidence intervals (the result of statistical calculations), along with the reported relative risks and odds ratios, and other details about each study as explained above and below. The concept of “statistical significance” is often misunderstood. In assessing any statistical evidence pertaining to medical issues, medical and scientific researchers note whether certain findings are “statistically significant.” However, findings that are not “statistically significant” are often statistically and clinically important and should be considered and weighed along with other available evidence in making causal assessments. The concept of statistical significance using arbitrary cutoffs has no relationship to the strength or direction of an estimated association, and may have very little relationship with the actual validity of a study’s results. A “P value” of 0.05 or less is often considered statistically significant, whereas 0.06 is not.² I agree with the epidemiologists who consider this “cut-off” to be arbitrary, because, for example, the .01 difference between $p = 0.05$ and $p = 0.06$ is essentially the difference between a 5% vs. 6% probability that the observed association is due to the role of chance. Even where a confidence interval includes “1,” depending on the values of the lower and upper bounds of the confidence interval, the most likely interpretation of the study results may be that there is an association between an exposure and the increased risk of a disease.

² In epidemiologic studies, epidemiologists or statisticians calculate a P-value and/or 95% confidence interval (“CI”) for each risk estimate. Essentially, the P-value and the CI assess the likelihood that the observed association is due to the play of chance. A 95% CI means that if the same experiment is repeated many times, 95% of the time, the true value of the risk estimate will fall between the upper and lower bound of the CI. The narrower the CI, the more precise and reliable the risk estimate is considered to be.

Bradford Hill stated that “[n]o formal tests of significance can answer those questions [of causation]. Such tests can, and should, remind us of the effects of the play of chance... Beyond that, they contribute nothing...” Therefore, in weighing the evidence, I note the P-value and/or the confidence interval reported with a study’s results, and consider this to be an important piece of information for interpreting study results. I do not think it is appropriate to disregard results just because they do not meet an arbitrary statistical threshold, a view also held by the American Statistical Association (Wasserstein 2016).

All observational studies have limitations, and the potential for “bias” and confounding. The presence of some bias is not generally a basis for scientists to disregard a study. Instead, when interpreting a study, biases must be considered and assessed for the likelihood that they may obscure, diminish, or magnify a study result, so the direction and magnitude of any bias must also be considered where possible. Some biases will have the effect of obscuring or understating an association between exposure and disease. Typically, study investigators will include as part of their published paper reporting the study results, the important strengths and limitations (including their assessment of the role of bias, chance and confounding) in the study.

In weighing the evidence, I also consider the likelihood that the study may understate or fail to detect an association that did exist (a Type II error, often due to lack of “power”); or the converse, that a study result may overstate an association or find an association that is not real (Type I error). In interpreting studies that do not report an association with an increased risk of ovarian cancer, one issue is whether the results provide reliable evidence of the absence of an association. The only way for data to provide statistical reassurance about the absence of an association is, in the absence of any important systematic error in the data, for the upper bound of a reasonable confidence interval (such as a 95% confidence interval) to be close to the null value.

When a study finds an association between exposure and disease, causation is one explanation, but it is not the only explanation. Other explanations must be considered and assessed. When an observational study results in a reported association between exposure and disease (i.e., relative risk or odds ratio greater than 1.0), and if alternative explanations (i.e., the role of bias, confounding and chance) are considered and determined to be unlikely explanations, then causation remains a likely explanation, subject to consideration of the Hill viewpoints. In order to reach an opinion that an association is causal between talc exposure and ovarian cancer, I considered whether there are other potential explanations that better explain the relationship and which are consistent with the totality of the scientific evidence. This assessment is informed by considering how a specific study fits into the overall totality of the evidence.

My opinions on causation are informed by a review of the strengths and limitations of the epidemiology evidence along with a review of other lines of evidence, including animal data and evidence on biological plausibility, likely mechanism(s) and dose/response. Thus, as part of my methodology, I have considered whether there is an alternative explanation to causation, based on an assessment of the totality of evidence. For example, I have considered whether the findings of the human epidemiologic studies are best explained by chance,

confounding or bias, when viewed separately, and most importantly, when viewed as a whole, and in light of the several lines of experimental evidence discussed in this report.

Based on my review of the totality of evidence, which I have weighed based on the considerations described above, I conclude with a high degree of medical and scientific certainty that exposure to talcum powder products can cause ovarian cancer. Causation is the best explanation for assimilating, assessing and weighing the totality of evidence. In reaching this opinion, I found it compelling that the epidemiologic studies that captured talc exposure consistently found an association between exposure to talc applied in the perineal area and epithelial ovarian cancer. The studies also provide persuasive evidence of a dose response effect, one of the viewpoints of causality discussed by Bradford Hill. There also is persuasive evidence of plausible and likely causal mechanisms for how talc exposure leads to ovarian cancer.

The other explanations for an association (other than causation) are bias, chance and confounding, and “reverse causation.”³ While it may not possible when looking at a single study to determine whether a recall bias, or a selection bias, or a potential confounder is materially affecting the results, I find it helpful to consider how each study fits into the whole. Here, multiple studies have been conducted in different populations, by different investigators, using different methods, and using different study types, and yet there is general consistency in the results. The vast majority of studies and meta-analyses find an association with an increased risk of ovarian cancer. Under these circumstances, viewing the evidence as a whole, the likelihood that the consistent finding of an association can be explained by bias, or chance or confounding is highly unlikely, especially in light of the results of the other lines of evidence.

Finally, as part of my methodology of considering alternative explanations for the evidence, I made an effort to understand the opinions of both the plaintiff and defense experts as concerning the issue of talc and causation of ovarian cancer. In that regard I have reviewed some plaintiff and defense expert testimony and reports, which are identified on my reference list. I also cited to the extensive medical literature I considered in connection with my work on this report.

IV. MECHANISM OF TALC’S CARCINOGENICITY

There is a plausible and likely biologic mechanism whereby talc causes inflammation which can lead to epithelial ovarian cancer. Chronic inflammation has been causally linked to a number of cancers. The evidence of the relationship between inflammation and cancer is based on many studies, including studies supporting the

³ In epidemiology, reverse causation is when the exposure-disease process is reversed; In other words, the exposure causes the risk factor. Here, the question is whether exposure to talcum powder products causes ovarian cancer or whether ovarian cancer causes increased usage of talcum powder products? I am not aware of any evidence to support a conclusion that reverse causation is a plausible explanation for the association between exposure to talcum powder products and ovarian cancer. The principal presenting symptom is abdominal bloating, which does not appear to lead to more talc use.

conclusion that inflammation plays a role in increasing the risk of epithelial ovarian carcinoma. As stated by the National Cancer Institute, “Over time, chronic inflammation can cause DNA damage and lead to cancer. For example, people with chronic inflammatory bowel diseases...have an increased risk of colon cancer.” The time interval between inflammatory response and presentation of cancer can be many years. Animal studies, particularly, may show granulomatous or other inflammatory reactions while not necessarily demonstrating neoplastic changes due to the time interval required for cancer to develop.

Studies have shown that pelvic inflammatory disease and endometriosis (known to cause an inflammatory reaction) increase the risk of ovarian cancer (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Lin 2011, Zhou 2017). Genofre et al. (2007) showed that talc can induce inflammation. Ness (1999) reported that inflammation of ovarian epithelium is a risk factor for ovarian cancer.

Inflammation has been implicated in carcinogenesis in several ways. Inflammation increases cytokines (Ness 1999). Shukla (2009) showed that nonfibrous talc can induce an inflammatory response that alters expression of genes in cancer pathways such as COX-2, ATF3, IL-6, and IL-8 in mesothelial cells. Further, inflammation increases oxidative stress (Ness 1999); Buz’Zard (2007) revealed that talc can induce oxidative stress and create reactive oxygen species (ROS), which in turn can induce ovarian neoplastic transformation in human ovarian cells. See also Saed (2017).

V. INFLAMMATION

Inflammation can produce toxic oxidants such as ROS that can be a source of mutagenesis to DNA. This damage to DNA by ROS is now accepted as a major cause of cancer, and has been demonstrated in ovarian cancer (Senthil 2004, Saed 2010, Saed 2017) as well as in breast and hepatocellular carcinoma (Waris 2006, Saed 2017). Talc exposure has been shown to cause a statistically significant increase in ROS in ovarian polymorphonuclear neutrophils (PMNs), resulting in a decrease in cell viability and neoplastic transformation of ovarian cells. The authors concluded that “talc increased proliferation, induced neoplastic transformation and increased ROS generation time-dependently in the ovarian cells.” (Buz’Zard 2007)

Thus, it is accepted that inflammation causes oxidative stress. Oxidative stress leads to the formation of ROS and reactive nitrogen species (RNS). Oxidative stress is an important factor in the initiation and development of several cancers, including ovarian cancer (Senthil 2004, Saed 2010, Saed 2018). The production of oxidants and free radicals affects cellular mechanisms that control cell proliferation and apoptosis, which in turn play a role in the initiation and development of several cancers (Saed 2018). ROS and RNS can induce genetic mutations and DNA damage, thus causing oncogenic phenotypes. Additionally, oxidative stress affects transcription factors that modulate the expression of genes important to the development and metastasis of cancer cells (Saed 2018). Oxidative stress is also known to activate certain signaling pathways, which are critical for the initiation and maintenance of the oncogenic phenotype (Waris 2006). In fact, the major source of cellular ROS, the NAD(P)H

oxidase family of enzymes, has been linked to the survival and growth of tumor cells in pancreatic and lung cancers (Reuter 2010, Rojas 2016). Pro-oxidant enzymes such as myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), and NAD(P)H oxidase have been associated with initiation, progression, survival, and increased risk in cancers such as breast, ovarian, lung, prostate, bladder, colorectal, and melanoma (Lengyel 2010, Fletcher 2017, Saed 2017, Saed 2018). Angiogenesis is critical for the survival of solid tumors and is also regulated by ROS (Reuter 2010, Saed 2017). Thus, it is clear that alteration of oxidative balance can provide an environment for cancer cell survival (Saed 2018).

Gene point mutations resulting in single nucleotide polymorphisms (SNPs), or a variation in a single base pair in DNA, have been associated with oxidative DNA repair genes and redox genes with cancer susceptibility (Klaunig 2010). There is evidence that genetic polymorphisms in genes with anti-tumor activity are associated with cell cycle genes and play a role in ovarian cancer etiology (Goode 2009, Notaridou 2011). There are associations of specific SNPs in oxidant and anti-oxidant enzymes with increased risk and survival of ovarian cancer (Belotte 2015, Fletcher 2017).

Higher levels of oxidants have been described in epithelial ovarian cancer (Malone 2006, Saed 2010, Jiang 2011). Fletcher et al. published an abstract in the March 2018 Reproductive Sciences that showed talc can generate a pro-oxidant state in both normal ovarian epithelial and ovarian cancer cells. In this study, there was a marked increase in mRNA levels of the pro-oxidant enzymes iNOS and MPO in talc treated ovarian cancer cell lines and normal ovarian epithelial cells, as compared to controls within 24 hours. There was also a marked decrease in the mRNA levels of the anti-oxidant enzymes catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase 3 (SOD3), but a marked increase in glutathione reductase (GSR) and no change in glutathione S-transferase (GST) in the talc treated ovarian cancer cell line and in normal ovarian epithelial cells compared to controls within 24 hours (Fletcher 2018). In addition to tumorigenic cells generating high levels of ROS that activate signaling pathways which promote proliferation, it is known that tumorigenic cells maintain a high level of antioxidant activity to prevent buildup of ROS to levels that could induce tumor cell death (Schieber 2014, Saed 2017).

ROS and RNS are normally neutralized by enzymes such as SOD, CAT, GST, glutathione (GSH), thioredoxin coupled with thioredoxin reductase, glutaredoxin, glutathione peroxidase (GPX), and GSR (Lei 2016). Glutathione S-transferase is involved in detoxification of carcinogens by catalyzing their conjugation to GSH (Lei 2016). The GS-X-MRP1 efflux pump, which removes toxins from cells, is known to be stimulated by the GSH/GSSG complex and this process has been investigated as a mechanism for the development of tumor chemoresistance (Ishikawa 1993, Circu 2012).

Further, data demonstrates that talc exposure caused a statistically significant increase in ROS in ovarian polymorphonuclear neutrophils (PMNs), which resulted in a decrease in cell viability and neoplastic transformation of ovarian cells (Buz'Zard 2007).

Additionally, inflammation induces increased cellular proliferation, giving rise to potential DNA replication errors. This is one of the ways increased lifetime ovulations increase the risk of epithelial ovarian carcinomas. Studies have shown that ovulation results in an inflammatory response to disruption of the ovarian epithelium with the release of inflammatory mediators that initiate cellular transformation and growth (Richards 2002). Endometriosis causes an inflammatory reaction (including macrophage activation, cytokine release, and expression of growth factors) and is a risk factor for clear cell (Figure 4) and endometrioid (Figure 5) ovarian carcinomas (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Edwards 2015). Studies have also shown that pelvic inflammatory disease (PID) is an ovarian cancer risk factor (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Lin 2011, Zhou 2017). Several prospective studies suggest that elevated serum levels of inflammatory markers such as CRP, TNF- α and IL-6 are predictive of development of ovarian cancer (McSorley 2007, Lundin 2009, Clendenen 2011, Toriola 2011, Poole 2013, Trabert 2014, Gupta 2016).

There also are some studies showing a protective effect of anti-inflammatory drugs on the risk of developing carcinoma, although some studies have failed to show a protective effect (Wu 2009). An analysis of many randomized controlled studies did show a reduced risk of developing carcinoma with aspirin use (Rothwell 2012). A 2014 article specifically evaluating ovarian carcinoma analyzed pooled data from 12 population-based case-control studies and showed a reduction of ovarian cancer risk with frequent aspirin and high-dose non-steroidal anti-inflammatory (NSAID) use (Trabert 2014). This further supports the role of inflammation in carcinogenesis, as this effect cannot be explained by other etiologies (Baandrup 2013, Trabert 2014).

Talc is not an inert substance. It has been shown to cause inflammation. Studies have shown increases in markers of inflammation following talc exposure (Allaire 1989, Genofre 2007, Arellano-Orden 2013). Talc is used therapeutically for patients with recurrent pneumothorax and pleural effusions based upon its ability to induce inflammation and adhesions. Injecting talc into the pleural space causes an inflammatory and granulomatous reaction, causing fibrosis and scarring which prevents further pneumothorax development (Antonangelo 2006, Najmunnisa 2007). This is mediated through the release of cytokines and chemokines (Nasreen 1998, van den Heuvel 1998), and the production of basic fibroblast growth factor (bFGF) (Antony 2004). It is worth noting that asbestos fibers are also known to initiate an inflammatory and scarring process within the pleura and peritoneum, which can eventually lead to neoplastic transformation of the mesothelium. The time interval between the initial inflammatory response for asbestos and talc and the development of cancer can be many years. Remote exposure will not necessarily mean there will be evidence of current inflammation or foreign body reaction when tissues are examined.

There also is evidence that talc induces macrophage TNF- α expression (Cheng 2000). Macrophages that express TNF- α promote ovarian tumorigenesis (Hagemann 2006). TNF- α is involved in chronic inflammation and induces mutations in vitro (Yan 2006). TNF- α induced chromosomal mutations occur mostly in cells with p53 aberrations (Yan 2006). Of note, high grade serous carcinomas typically have inactivating mutations in p53. Both talc and TNF- α induce macrophage expression of IL-8 (Nasreen 1998, van den Heuvel 1998), which attracts

neutrophils that then release ROS. This in turn causes a feedback loop between ROS generation and increased TNF- α expression, causing increased DNA damage (Xie 2000). This is an important line of biological experimental evidence supporting my causation opinion. The strongest association of talc and ovarian cancer is with invasive serous carcinomas, which commonly have p53 mutations, and TNF- α induced chromosomal mutations occur mostly in cells with p53 aberrations. Talc has been shown to induce macrophage TNF- α expression, which has been shown to promote ovarian tumorigenesis.

VI. ROLE OF IMMUNE SYSTEM IN CARCINOGENESIS

Studies have evaluated the protective role of the immune system in carcinogenesis, and in particular anti-MUC1 antibodies (Cramer 2005). MUC1 is a high molecular weight transmembrane protein expressed in many normal organs in a highly-glycosylated form. In cancer, including ovarian carcinoma, MUC1 is expressed at high levels in a poorly-glycosylated form. Anti-MUC1 antibodies are produced when high levels of the poorly-glycosylated form of MUC1 present to the immune system. Anti-MUC1 antibodies have been found in some cancers (Ho 1993, Dong 1997, Feng 2002) and have been associated with improved prognoses (Kotera 1994). Chronic processes including endometriosis, ovulation and talc exposure affect expression of MUC1 (Cramer 2005, Vlad 2006, Terry 2007). Decreased anti-MUC1 antibody production caused by these processes plausibly leads to immune-tolerance of an early ovarian carcinoma. Cramer et al. published a paper in 2005 that showed factors which increase the levels of anti-MUC1 antibodies lower the risk of ovarian carcinoma (Cramer 2005). Factors that decrease anti-MUC1 antibodies, such as incessant ovulation, have been associated with an increased risk of ovarian carcinoma (Terry 2007). Prospective data from the Nurses' Health Study (NHS) showed that tubal ligation increases anti-MUC1 antibodies, potentially by the procedure triggering the production of anti-MUC1, thus indicating another way tubal ligation exerts its protective effect. The study also showed that increased numbers of ovulatory cycles decrease anti-MUC1 antibodies, providing an explanation for the increased risk of ovarian cancer with increased lifetime ovulations (Pinheiro 2010). These studies provide evidence that MUC1 antibodies serve a role in the mechanism of and immune response in ovarian carcinogenesis. Because talc use is associated with a decrease in MUC1 antibody expression, the above is relevant to assessing the risk of talc use and ovarian cancer and provides further evidence supporting causation.

VII. COSMETIC TALC

Cosmetic talc has been used for decades, applied directly or indirectly to the genital region because of its high absorbency and softness (Langseth 2008).

Talc is a magnesium silicate hydroxide, characterized by water molecules in between silicate sheets. Asbestos is also a silicate mineral, but is somewhat morphologically distinct from talc and belongs to different silicate mineral groups. However, the chemical similarity of asbestos and talc led some researchers to postulate that both talc and asbestos could be causes of ovarian cancer (Graham 1967, Henderson 1971, Longo 1979). Early research into the possible link between talc and ovarian cancer was also instigated due to the fact that high

grade serous carcinoma, a type of invasive serous epithelial ovarian cancer (Figure 1), shown to be most commonly associated with perineal talc use, has striking morphologic similarities to mesothelioma (Figure 2), the tumor most associated with asbestos (Graham 1967). High grade ovarian serous carcinoma and mesothelioma express similar immunohistochemical markers, most notably cytokeratin pattern, WT-1 and calretinin. In fact, a great deal of surgical pathology literature deals with the nuances in differentiating peritoneal mesothelioma from high grade serous carcinoma. In the last few years, additional immunohistochemical panels have been developed that help distinguish between these two tumors (Laury 2010, Ordonez 2013), including PAX8, which is also expressed in fallopian tube epithelium. The morphologic and immunohistochemical similarities between asbestos and talc malignancies constitute another line of evidence supporting my opinion that talc exposure in the genital area causes ovarian cancer. Later in this report, I address the evidence that asbestos exposure can cause ovarian cancer.

VIII. TALC MIGRATION, TRANSLOCATION, INHALATION, AND LYMPHATIC TRANSPORT

In order for cosmetic talc applied to the perineum to reach the ovary or fallopian tube and exert a neoplastic effect, it needs to travel up through the vagina and uterus. It is known that substances can travel proximally through the female genital tract to the fallopian tubes and ovaries (Egli 1961, Venter 1979). Several studies have demonstrated the presence of talc in ovarian tissue (Henderson 1971, Henderson 1979, Mostafa 1985, Heller 1996) and even in the pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc (Cramer 2007). This is evidence that talc can be transported through the lymphatic system. Thus, another biologically plausible pathway is inhalation leading to lymphatic transport to the ovaries (Suzuki 1991, Marchiori 2010, Frank 2011).

There is evidence that serous ovarian cancers are actually of fallopian tube origin (Piek 2003, Kindelberger 2007, Kurman 2010, Erickson 2013). When considering whether talcum powder can cause ovarian cancer, this consideration is not critical. Talcum powder particulates reach both the fallopian tubes and ovarian surfaces by migrating proximally.

IX. TALC IN TISSUE

As mentioned above, several studies have demonstrated the presence of talc in ovarian tissue (Henderson 1971, Henderson 1979, Mostafa 1985, Heller 1996) and one study found talc in the pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc (Cramer 2007). In Cramer et al.'s 2007 paper, the methods used by Dr. John Godleski to identify talc particles in tissue are outlined (Cramer 2007).

Tissue was first analyzed using polarized light microscopy to identify birefringent particles within the tissue plane. Polarized light microscopy is used in routine practice in anatomic pathology. One of the most common uses in surgical pathology is for the identification of calcium oxalate calcifications in breast tissue. In some lesions of the breast,

ranging from benign to malignant, calcifications occur that can be a marker for disease and are discovered on breast mammography. After mammography reveals calcifications and the radiologist determines them to be suspicious for disease, the area with calcifications is biopsied. The biopsy sample is then X-rayed to confirm the presence of the calcifications, and then submitted to the pathology laboratory for histologic analysis and diagnosis. The pathologist correlates the calcifications seen under the microscope with those in the specimen X-ray to be sure the calcifications the radiologist identified are visualized in the tissue sample. Calcium oxalate is a certain type of calcification that is not easily seen on light microscopy. If there appears to be a discrepancy between the tissue under light microscopy and the specimen X-ray (lack of calcifications under light microscopy), the pathologist will use polarized light microscopy to help identify calcium oxalate crystals, which are birefringent. Similarly, Dr. Godleski used polarized light microscopy to identify birefringent material that could be further analyzed using SEM and EDX.

SEM was more commonly used in surgical pathology before immunohistochemical studies were routinely used and before the common availability of molecular testing. However, SEM is still routinely used as an important diagnostic tool in areas of pathology in which immunohistochemical studies and molecular testing are less helpful, such as medical renal pathology, neuromuscular disorders and rare tumors. SEM uses electrons for imaging, analogous to light microscopy using light. SEM allows for much greater magnification (>100,000X) than light microscopy.

EDX is a qualitative and quantitative chemical analysis used in conjunction with SEM. It detects X-rays emitted from the sample during electron scanning to determine the elemental composition of the particle being examined. EDX is widely used in many biomedical areas, as it provides precise information on the chemical composition of subcellular structures that can be correlated with their SEM images (Wyroba 2015).

In Cramer et al 2007, the authors analyzed four pelvic lymph nodes from a 68 year old woman with ovarian papillary serous carcinoma and a small component of clear cell carcinoma. She had been a daily talc user for 30 years, having applied it to underwear and sanitary napkins. The lymph nodes showed birefringent particles via polarized light microscopy and were then analyzed by SEM and EDX. This showed magnesium and silicate signatures consistent with talc (Cramer 2007). Of note, there are similar studies performed with asbestos fibers in tissue sections (Roggli 1983, 1986).

Additionally, studies have shown Raman microscopy can be used to identify talc spectra in routinely processed, but unstained, histologic pathology specimens. Raman microscopy uses laser light to elicit the chemical and microstructural characterization of materials (Campion 2018).

Although the presence of talc particles found in ovarian cancer tissue does not prove that the talc played a causal role, when considered with the other lines of evidence supporting causation discussed in this report, the presence of talc in ovarian cancer tissue is certainly consistent with causation and provides additional evidence in support of a causal relationship between talcum powder products and ovarian cancer.

X. EPIDEMIOLOGICAL DATA REGARDING TALC USE AND OVARIAN CANCER:

As detailed below, there is consistent evidence from multiple observational studies, pooled analyses, and meta-analyses that exposure to talcum powder products is associated with an increased risk of ovarian cancer. When combined and considered with the biological evidence described above, this consistent epidemiologic data from multiple studies provides strong evidence that the association is, in fact causal.

Although occasional studies have not found talc powder applied to the perineum or contraceptive diaphragms⁴ to be a significant risk for developing ovarian cancer, as detailed below, most have found an association, and the cumulative evidence from these studies, when considered with the other lines of evidence discussed above, provides strong and compelling evidence of a causal association.

XI. CASE-CONTROL STUDIES

Henderson first observed talc particles embedded in both ovarian tumors and normal ovaries (Henderson 1971). The first epidemiologic study on genital talc use and the risk of ovarian cancer was a case-control study by Cramer et al. (Cramer 1982). In this study, 215 women with epithelial ovarian cancer and 215 age-matched controls were questioned about talc use on the perineum and/or on sanitary napkins; 42.8% of ovarian cancer patients reported regular use of talc (prior to developing ovarian cancer) compared to 28.4% of controls, with an odds ratio (OR) of 1.92 (95% confidence level (CI) 1.27-2.89). The greatest risk in this study occurred in women who had used talc powder both directly on their perineum and on sanitary napkins compared to women who had no history of talc powder use; the odds ratio was 3.28 (CI 1.68-6.42). Of note, Cramer et al. did not exclude women from the control group who had a history of hysterectomy or other “pelvic surgeries” if the patient had intact ovaries by self-report. This could potentially lead to an underestimate of the risk of talc and ovarian cancer, as the controls may have had other confounding factors. They did control for confounding factors such as age, parity, religion, education, age of menarche, oral contraceptive use, hormone replacement therapy and smoking history.

While case control studies may have limitations with selection bias, Cramer et al. state “Our sample of cases represents more than 50% of ovarian cancer cases diagnosed

⁴ It is likely that studies based on talc with diaphragm use are generally limited to use by women for birth control purposes. This will not capture use before or after the women’s use of diaphragms for contraceptive purposes, a potential of multiple years that will not be captured in the study. Even for the years when women are using diaphragms, it is likely they are not using diaphragms for birth control on a daily basis. Therefore, diaphragm studies are likely to be biased toward the null; i.e., likely to understate talc exposure, and for that reason are likely to fail to detect an association that actually exists or understate the magnitude of risk.

in Boston residents in the study period. Therefore, it is difficult to conceive of a plausible bias in the selection of cases that would yield this excess use of talc.” (Cramer 1982)

In additional to the Cramer 1982 study, numerous other case-control studies addressing talc use and ovarian cancer have shown statistically significant odds ratios greater than 1, indicating talc use is associated with an increased ovarian cancer risk (Harlow 1989, Booth 1989, Harlow 1992, Chang 1997, Cook 1997, Green 1997, Godard 1998, Cramer 1999, Gertig 2000, Ness 2000, Mills 2004, Merritt 2008, Wu 2009, Moorman 2009, Rosenblatt 2011, Kurta 2012, Houghton 2014, Wu 2015, Schildkraut 2016, Cramer 2016).

In a 1983 letter to the editor in JAMA in response to the 1982 Cramer study, Hartge and Hoover state that they found an association between genital talc use and ovarian cancer with a RR of 2.5, but the sample size was small (7 cases to 3 controls), resulting in a wide confidence interval (0.7-10.0). They did not find an association between ovarian cancer and body talc use or talc use on diaphragms, but again the sample sizes were small (Hartge 1983). Similarly, a study published by Tzonou et al. in 1983 showed no association between perineal talc use and ovarian cancer (RR 1.05; CI 0.28 to 3.98) but the frequency of reporting talc use was low in the study population, thus the wide CI (Tzonou 1983).

Whittemore et al. published a case-control study in 1988 that showed a RR of perineal talc use and ovarian cancer of 1.40, with a p value of 0.06. They did not see an increased risk of ovarian cancer in women who used talc on sanitary napkins or diaphragms. They did see an increased risk of ovarian cancer in women who used perineal talc for 1 to 9 years compared to those who used it for a shorter period (RR 1.60, p=0.05, CI 1.00-2.7) but did not see an increase with perineal talc users greater than 10 years (RR 1.11, p=0.61, CI 0.74-1.65). A strength of this study is that participants were not only asked about their history of talc use, but also about their history of cigarette smoking, coffee and alcohol consumption, thus addressing recall bias. A possible limitation of this study is the fact that the control group was a combined group of two separate control groups: one hospital based from the hospitals where the cases were admitted, and one community based. It was not described for what conditions the hospital controls were admitted (Whittemore 1988).

In 1989 Booth et al. published a study that showed an increased risk of ovarian cancer in daily talc users (RR 1.3, CI 0.8-1.9) and weekly talc users (RR 2.0, CI 1.3-3.4) as opposed to monthly (RR 0.7, CI 0.3-1.8) and rare (RR 0.9, CI 0.3-2.4) users. There were limitations of this study, however; participants were limited to women younger than 65 who had been diagnosed within the two years prior to interview. The data was adjusted for age in 5 year stratas and socio-economic status, but socio-economic status was based upon husband’s career if married and participant’s career if never married. Strengths, however, included queries of hormone replacement therapy, type of contraceptive use, and duration of oral contraceptive use; this helps to address recall bias. Additionally, hospital-based controls admitted for gynecologic disease and breast cancer,

among other diseases, were excluded and hospital admission diagnoses were listed (Booth 1989).

Harlow's 1992 study included 235 women with epithelial ovarian cancer and compared them to 239 control women matched for age, race and residence. After adjusting for age, parity, weight, education, marital status, religion, use of sanitary napkins and douching, it was found that talc use increased the ovarian cancer risk by 50% (OR=1.5, CI 1.0-2.1). Harlow's 1992 study also involved a dose-response effect; duration and frequency of perineal talc use was calculated into lifetime talc applications. Lifetime application ORs, when compared to control women with no perineal talc exposure, were 1.3 for <1000 (CI 0.7-2.7), 1.5 for 1000-10,000 (CI 0.9-2.4) and 1.8 for >10,000 (CI 1.0-3.0) (Harlow 1992). A dose response effect is a consideration in assessing causation. Harlow, Terry (2013) and Wu (2015) studies provide clear evidence of a dose effect. Particular strengths of the Harlow study are the number of potential confounding factors adjusted for and the detailed history on type of use and duration of use. Women with body exposure (non-genital) were considered non-exposed. Additionally, in the Harlow study, women were also asked about dietary and smoking histories, which helps to address potential recall bias.

Rosenblatt et al. published a study in 1992 that showed an increased risk of ovarian cancer with talc use (OR 1.7, but a small sample size with CI 0.7-3.9) (Rosenblatt 1992). In the Rosenblatt study, participants were also asked about oral contraceptive use and hormone replacement therapy, which helps to address potential recall bias. Another study published in 1992 by Chen et al. evaluated the association between talc use and ovarian cancer in a Beijing population. They found a RR of 3.9 in women with a history of use greater than 3 months, but the sample size was small with a 95% CI of 0.9-10.63. They also included dusting powder to the lower abdomen as well as perineum (Chen 1992), which would likely understate the magnitude of the association.

A 1997 study published in the journal *Cancer* by Chang et al. analyzed 450 patients with either ovarian borderline tumors or invasive ovarian carcinomas and showed an increased risk of tumor in women with either direct perineal application of talc or talc use on sanitary napkins (OR=1.42 after adjusting for age, parity, tubal ligation, hysterectomy, duration of oral contraceptive use, length of breastfeeding after pregnancy, and family history of ovarian cancer CI 1.08-1.86). For invasive ovarian carcinomas, the adjusted OR was 1.51 (CI 1.13-2.01). For borderline tumors, the adjusted OR was 1.24 (CI 0.76-2.02) (Chang 1997). The authors found that a borderline-significant association between duration of talc exposure and risk (OR 1.09, 95% CI 0.98-1.21, per 10 years of exposure). No significant association was found between frequency of exposure and risk. In comparing invasive and borderline carcinomas, risk remained elevated for both carcinoma types. The study did not assess for non-genital talc use. A particular strength of this study is that the same questions regarding talc use were asked about cornstarch use; they found no significant risk of ovarian cancer with cornstarch use (OR 0.31, CI 0.06-1.66), although only 1% of the populations reported using cornstarch (Chang 1997). Still, this helps to reconcile potential confounding risk factors of ovarian cancer in people more likely to use perineal powder. The interviews with participants also included taking

histories on oral contraceptive use and hormone replacement therapy, which helps to address recall bias.

Cook et al. also published a study in 1997 that evaluated 313 women with epithelial ovarian tumors (both invasive and borderline) and 422 controls. Only white women were included. They found that there was an increased risk of ovarian cancer with direct perineal powder dusting of 60% (OR=1.6, CI 1.1-2.3) and 90% (OR=1.9, CI 1.1-3.1) for genital deodorant sprays sprayed directly onto the perineum. Lifetime number of talc applications provided evidence of dose-response: a statistically significant increased risk (OR=1.7, CI 1.0-2.9 for less than or equal to 500 applications, OR=2.6, CI 0.9-7.6 for greater than 500 applications). A strength of this study is that participants were asked about smoking and contraceptive use, which helps to address recall bias. A limitation of this data is that all types of powder were included, such as cornstarch, "baby powder," "deodorant powder," and "scented body/bath powder." However, the authors state, "No specific type of powder used for perineal dusting, diaphragm storage, or on sanitary napkins was strongly related to ovarian cancer risk, although there was a suggestion of an elevated risk associated with any use of talcum powder and bath/body powders (RR = 1.6, 95 percent CI 0.9-2.8, and RR = 1.5, 95 percent CI 0.9-2.4, respectively)." (Cook 1997)

In 1997, an Australian study performed by The Survey of Women's Health Study Group enrolled 824 women with epithelial ovarian tumors, both invasive and borderline, and 855 controls. They found that the risk of ovarian cancer was highest among women who were talc users and had not undergone surgical sterilization (RR=1.3, CI 1.1-1.7) after adjusting for age, parity, duration of oral contraceptive use, BMI, smoking, education and family history of ovarian cancer. The risk was lowest in women who had not applied talc to their perineum and had either a tubal ligation or hysterectomy (RR=0.6, CI 0.50-0.84) (Green 1997). Because tubal ligation limits transport of talc fibers to the ovary, this study, with a finding of a protective effect in women with tubal ligation, provides an important piece of additional evidence. Strengths of this study include high response rate (90% of cases and 73% of eligible controls) and the verification of past surgical procedures by contacting participants' surgeons. Additionally, participants were asked questions about other potential exposures such as smoking histories and pelvic inflammatory disease, which helps to address recall bias. Limitations include a lack of data on quantity of talc use.

In 1999, Wong et al. published a paper that did not show a consistent association with talc powder and ovarian cancer, evaluated by length of use as follows: talc use for 1-9 years (OR 0.9; 95% CI 0.6, 1.5), 10-19 years (OR 1.4; 95% CI 0.9, 2.2), or more than 20 years (OR 0.9; 95% CI 0.6, 1.2). This was after adjustment for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy. However, this study would tend to understate the magnitude of an association with genital talc use because it included talc use on thighs as well as genitals. The study used hospital controls, which raises a question of whether the controls were comparable to the cases (Wong 1999).

As part of Cramer et al.'s 1999 study, 563 women with newly diagnosed epithelial ovarian cancer were compared to 523 controls, and showed that perineal talc users had a significantly increased odds ratio for epithelial ovarian cancer (OR=1.60, CI 1.18-2.15). The effect of talc use was even stronger for invasive serous carcinoma (OR=1.70, CI 1.22-2.39). This was after adjusting for age, parity, oral contraceptive use, body mass index and family history of breast or ovarian cancer. The higher risk for women with invasive serous carcinoma was replicated in other studies, and this is an important finding in these studies because of its specificity. In addressing potential recall bias, Cramer et al. state, "...recall bias seems more likely to affect exposures that have occurred over a short term than those that have occurred over a long term. Since average duration of talc use exceeded 20 years in both cases and controls in our current study, genital talc exposure may be less likely to be subject to recall bias... It also seems reasonable that selective recall would lead to cases reporting all types of talc exposure more frequently than controls, but our study found that cases did not report a significant excess of talc use in non-genital areas compared to controls. Finally, if recall accounted for the association, one would expect little variation in the odds ratios by histologic type of ovarian cancer.... Regarding potential bias from confounding, we found no evidence that genital talc exposure varied by key risk factors for ovarian cancer such as age, parity or [oral contraceptive] use and little variability of the association by these and other variables." (Cramer 1999)

Ness et al.'s 2000 study evaluated 767 women with ovarian epithelial borderline tumors and ovarian invasive cancer compared to 1367 controls. Consistent talc use, defined as at least once per month for six or more months, increased the ovarian cancer risk by 50% (OR=1.5, CI 1.1-2.0) when applied to the perineal area directly and increased the risk by 60% (OR=1.6, CI 1.1-2.3) when used on sanitary napkins. This is after adjusting for age, parity, tubal ligation, hysterectomy, duration of oral contraceptive use, breast feeding and family history of ovarian cancer (Ness 2000). One explanation of the increased risk of talc use on sanitary napkins is that sanitary napkins may keep a larger amount of talc closer to the vagina over the course of several hours, thus increasing the risk of entry to perineum, while talc directly applied to the perineum may more easily disperse, however, many studies have failed to show an increased risk in ovarian cancer in participants whose only exposure to talc was on sanitary napkins. The strengths of this study include addressing multiple confounding factors. No dose-response was found; weaknesses include that only duration information was available, and genital/rectal talc use durations reported were combined with duration of use on the feet. Additionally, women who used just once per month were categorized as a user. These weaknesses may cause an underestimation of risk, and may have accounted for the lack of dose-response found.

Mills et al. published a study in 2004 that evaluated the association between talc use and ovarian cancer among 256 cases of ovarian cancer as compared to 1122 controls. Women diagnosed with invasive epithelial ovarian cancer with a history of genital talc use had an increased risk of 51% (OR=1.51, CI 1.07-2.12). This increased risk increased to 77% (OR=1.77, CI 1.12-2.81) for women diagnosed with invasive serous carcinoma.

Dose-response effects were also found. Increasing frequency of use was associated with increasing risk; women who reported use 4–7 times per week had a 74% elevation in epithelial ovarian cancer risk (p for trend = 0.015). However, the risk decreased between the second and third categories of use (from “rarely to several times per month” and “1-3 times per week” at 1.34 (CI 0.87-2.08) to 1.16 (CI 0.74-1.81), respectively). Duration of use of talc was also associated with increased risk, although the risk peaked among those reporting 4–12 years of use and declined somewhat among those reporting longer duration of use (p for trend = 0.045). Cumulative use also demonstrated an uneven association with risk of epithelial ovarian cancer in that the point estimates peaked in the second and third quartiles of intensity but declined in the highest quartile of use. These findings were after adjusting for age, race/ethnicity, duration of oral contraceptive use and duration of breast feeding. Yet, there wasn’t adjustment for first relative history of breast or ovarian cancer, pregnancy history, parity, BMI, hysterectomy, tubal ligation or hormone replacement therapy; according to the authors, the Hosmer-Lemshow goodness-of-fit tests revealed that after terms for duration of oral contraceptive use and duration of breast-feeding were added to the models, fit was not improved by the addition of these variables, nor were the estimated odds ratios altered by the addition of several of these variables (Mills 2004). However, the fact that participants were queried about other possible exposures such as hormone replacement therapy helps to address potential recall bias.

In Wu et al.’s 2009 study, women were found to be at increased risk of ovarian cancer if they had a history of prior perineal talc use, with the risk increasing significantly in those with long term (20+ years) and frequent (at least daily) use with a relative risk of 2.08 (CI 1.34-3.23), i.e., a dose effect. The authors did find an increased risk in women who used talc on sanitary napkins (RR 1.61, CI 0.93-2.78), underwear (RR 1.71, CI 0.99-2.97) and diaphragms/cervical caps (RR 1.14, CI 0.46-2.87). There was a stronger association between talc use and serous ovarian cancer; the relative risk with any talc use was 1.70 (CI 1.27-2.28). Strengths of this study include the adjustment for multiple possible confounding factors (age, race/ethnicity, education, age of menarche, parity, oral contraceptive use, family history of ovarian or breast cancer, menopausal status and tubal ligation). Another strength was that participants were queried about NSAID and endometriosis histories, helping to address potential recall bias. The authors mention in their discussion that the participation response was “modest,” possibly leading to selection bias (Wu 2009).

Rosenblatt et al. published a study in 2011 that showed an overall increased risk of ovarian cancer in women who used talc after bathing (OR=1.27, CI 0.97-1.66) with a more pronounced risk in women diagnosed with mucinous borderline tumors (OR=1.78, CI 0.98–3.23) and serous borderline tumors (OR=1.47, CI 0.85-2.55) (serous borderline tumor illustrated in Figure 3). They did not see an increased risk by extent of use, defined as years in which powder was used, or as lifetime number of applications. There was no alteration in the risk of ovarian cancer associated with other types of powder exposure such as sanitary napkins or diaphragms. This study did not find an increased risk of invasive serous carcinoma (OR 1.01, CI 0.69-1.47). (Rosenblatt 2011) A strength of this

study is that participants were queried about other potential exposures (smoking, alcohol and endometriosis histories), which helps to address recall bias.

In 2012, Kurta et al. evaluated talc use and the risk of ovarian cancer, although their main focus of the study was the associated risk of ovarian cancer with fertility drug use. They found a OR of 1.40 (CI 1.16-1.69). Since talc was not the primary focus of this study, duration of use was not considered; participants were categorized as talc users if they had ever used talc versus never-users. Perineal talc use was only generally defined as dusting powder or deodorizing spray on the genital or rectal areas, sanitary napkins, underwear, or diaphragms or cervical caps (Kurta 2012). A strength of this study is that its main focus was on fertility drug use; participants were asked about exposures such as fertility treatments and hormone replacement therapy, which helps to address potential recall bias.

Wu et al. published a paper in 2015 that evaluated talc use and invasive ovarian cancer in white, Hispanic and African American women. They found that talc use was more common in African-American women (44.1%) than in non-Hispanic whites (30.4%) or Hispanics (28.9%) ($p=0.001$). The results showed ORs of 1.41 for white women (CI 1.21-1.67), 1.77 for Hispanic women (CI 1.20-2.62) and 1.56 for African American women, although the CI for African American women was 0.80-3.04. Overall, the OR was 1.46 (CI 1.27-1.69). However, the response rate and sample size for this study was somewhat small, and participants with less than one year of use were categorized as never users (Wu 2015).

In 2016, Schildkraut et al. published a paper as part of the African American Cancer Epidemiology Study (AACES), a case-control study of epithelial ovarian cancer in African American women. According to the authors, due to the relatively small number of women who reported having only used genital powder (43 cases and 44 controls), the authors merged this exposure category with those who reported use of both non-genital and genital powder, creating an exposure category of “any” genital powder use, but separately evaluated the categories as “only” or “any” genital powder use. They reported an increased risk of ovarian cancer in “any” genital powder users (OR=1.44, CI 1.11-1.86) and noted a statistically significant dose response effect for both duration of use and lifetime applications. A strength of this study was adjustment for multiple confounding factors such as age, education, BMI, parity, tubal ligation, OCP use, first degree relative with breast or ovarian cancer, and interview year (taking into account litigation cases in the year 2014). Participants were also asked about hormone replacement therapy, another potential exposure, thus helping to address potential recall bias. A weakness of this study is that participants were considered “regular users” if they reported using cornstarch, baby or deodorizing powders at least one time per month for at least 6 months, and “never users” if they did not, leading to possible misclassification that would bias toward the null (Schildkraut 2016).

The totality of the results of the case-control studies support a causal link between talc and ovarian cancer. When observational studies find an increased risk of disease with a certain exposure, the possible reasons are chance, bias, confounding and causation.

There is a general consistency of these individual studies; the ORs have been of similar magnitude in studies spanning different decades, in different populations, with different study designs, by different investigators, over different continents and with adjustment for multiple confounders. Therefore, the possibility that the association between perineal talc use and ovarian cancer is due to chance is extremely unlikely.

Although retrospective case-control studies potentially have an element of recall bias and other potential biases, again, the consistency of results across these studies and populations makes recall and other bias an unlikely explanation. During the period that the majority of studies were conducted, public awareness of the link between talc and ovarian cancer was limited. There is also a much stronger and statistically significant association of perineal talc use and ovarian cancer in studies that compared all-body talc use to perineal use. The finding in some studies that serous carcinoma has a stronger association with perineal talc exposure than other histologic subtypes of ovarian cancer also argues against recall bias, as participants are very unlikely to have knowledge about the histologic subtyping of ovarian cancer. In addition, in studies where participants are asked to recall multiple exposures, not just talc exposure, this will minimize the risk of recall bias because it is unlikely that participants will differentially recall talc exposure but not other exposures, especially if they are blinded to the study hypothesis. Studies using trained interviewers, structured interview questionnaires, and blinding of both study participants and the interviewers to the study hypotheses will also limit the potential for recall bias.

Selection bias (which can arise based on differential participation rates or other differences between comparison groups) accounting for the results across studies is also unlikely. To see such consistent associations between perineal talc use and ovarian cancer, there would need to be strong associations between participation and perineal talc use, and strong differences amongst cases and controls due to selection bias only - this would be extremely unlikely to produce such large biases across studies. Most studies adjusted for confounders, with the majority adjusting for age, BMI, and parity among others. With chance, bias, and confounding being unlikely explanations for the association of perineal talc use and ovarian cancer across multiple studies, this leaves causation as the most likely explanation.

XII. COHORT STUDIES

The talc literature includes several cohort studies reporting the relative risk for perineal talc use and risk of ovarian cancer, including the Nurses' Health Study, the Women's Health Initiative and the Sister Study (Gertig 2000, Gates 2008, Gates 2010 and Gonzalez 2016). There were several important limitations of these studies to adequately capture risk of ovarian cancer based on the methodology used by the researchers to assess talc exposure.

The Gertig study evaluated prospective cohort data from 78,630 women, and although there was a 12% overall increased risk of ovarian cancer in women with a history of daily genital talc use, this was not statistically significant. Yet, the investigators

reported a statistically significant increased risk of invasive serous carcinoma (RR=1.4, CI 1.02-1.91) after adjusting for age, parity, duration of oral contraceptive use, post-menopausal hormone use, tubal ligation, BMI and smoking (Gertig 2000). Additionally, the lack of statistical significance of overall ovarian cancer risk may be due to several important limitations with this study, including the fact that the question of talc use was only in one questionnaire in 1982 and did not include questions on duration of use. Thus, a person who used talc just a few times would be included with women who used talc daily over a long duration, and this will have the effect of understating the risk. In fact, in a follow-up 2008 report, Gates et al. noted that since talc exposure was only referred to once in questionnaires, it is possible that some participants were misclassified with respect to their talc use or that some women may have started talc use after 1982 and thus these women would not be included in the talc user group (Gates 2008). This would understate the risk and decrease the calculated statistical significance of talc-related ovarian cancer. An additional review of the Nurses' Health Study published by Gates et al. in 2010 studied 876 cases of ovarian cancer and talc use, although this was not the primary focus of the study. This study found an overall increased risk of ovarian cancer with talc use (RR=1.06), but found an increased risk for mucinous tumors (RR=1.50) (Gates 2010) (mucinous carcinoma illustrated in Figure 6). Again, the weaknesses in the study include the fact that talc use was only queried once in 1982, and the authors state themselves that the limited data on talc use may have influenced the observed association with ovarian cancer.

Cohort studies like the Nurses' Health Study, Women's Health Initiative Study and the Sister Study have some drawbacks when studying rarer diseases compared to case-control studies that have been described above. Cohort and case-control studies are both observational, and both have strengths and limitations. Cohort studies begin when all participants are free of the disease in question. After a follow-up period, those that have the disease being studied are compared by exposure risk being studied to those who did not develop the disease. Although this helps to ensure exposure predates disease, there may be a lack of data if the disease is rare or if there is a long latency period between exposure and disease presentation/diagnosis, as is the case of ovarian cancer and talc. In contrast, in case-control studies, patients already have the disease being studied and are compared to controls who do not have the disease with a focus on the rates of exposure to the agent of interest (here, talcum powder products) in the cases as compared to the controls. A possible limitation of case-control studies in the context of ovarian cancer and talc is the fact that exposure to talc is self-reported and subject to potential recall bias.

The case-control studies may unavoidably have recall bias, as talc use was self-reported by participants. In their 2018 meta-analysis discussed below, Penninkilampi et al. noted that in some studies, interviewers were not blinded to cases and controls and many studies did not describe whether their controls had a personal history of previous ovarian cancer. However, they also noted that in general, controls were well matched to cases by other possible confounding factors such as age, geographic, location and ethnicity (Penninkilampi 2018).

In the 2008 Gates paper, women with certain variants in glutathione S-transferase M1 (GSTM1) and/or glutathione S-transferase T1 (GSTT1) were shown to have a higher risk of talc-associated ovarian cancer. Glutathione S-transferases catalyze the conjugation of glutathione to numerous potentially genotoxic compounds. Individuals with homozygous deletions of GSTM or GSTT have reduced or no glutathione S-transferase activity and may be unable to eliminate electrophilic carcinogens as efficiently (Coughlin 2002). The 2008 Gates study included 1,175 cases and 1,202 controls from a case-control study and 210 cases and 600 controls from the prospective Nurses' Health Study. Participants were genotyped for the GSTM1 and GSTT1 gene deletions and three NAT2 polymorphisms. Regular talc use was associated with increased ovarian cancer risk in the combined study population (relative risk=1.36, CI 1.14-1.63; p-trend<0.001). In the pooled analysis, the association of talc and ovarian cancer was stronger among women with the GSTT1-null genotype (p-interaction=0.03), particularly in combination with the GSTM1-present genotype (p-interaction=0.03). There was no clear evidence of an interaction with GSTM1 alone or NAT2. Without talc exposure, these genes were not clearly associated with risk of ovarian cancer (Gates 2008). The specificity of the findings linking the genetic polymorphisms with ovarian cancer subtype most associated implicates yet another aspect of the Bradford Hill viewpoints.

As previously detailed, the Nurses' Health Study also showed that genital talc use was associated with lower levels of anti-MUC1 antibodies, which has been associated with an increased risk of ovarian cancer. As part of the Nurse's Health Study, Pinheiro et al. published a paper in 2010 that showed increasing anti-MUC1 antibody levels were associated with a nonsignificant trend for a lower risk of ovarian cancer with highly significant heterogeneity by age (p-heterogeneity=0.005). The authors concluded that anti-MUC1 antibodies evaluated several years prior to diagnosis may be associated with lower risk of subsequent ovarian cancer in women less than 64 years old at assessment (Pinheiro 2010). Cramer et al. 2005 study showed factors which increase the levels of anti-MUC1 antibodies lower the risk of ovarian carcinoma (Cramer 2005). These findings provide evidence that a plausible mechanism for talc-associated ovarian cancer is a down-regulated immune response to MUC1, and thus an immune tolerance of an emerging MUC1-expressing tumor.

The Women's Health Initiative Observational Study (WHI-OS) did not report a statistically significant increased risk of ovarian cancer with talc use (Houghton 2014). In that study, 61,576 women were enrolled and 429 developed ovarian cancer during follow-up. The study did find a 12% increased risk of ovarian cancer in perineal talc users (RR=1.12, CI 0.92-1.36), but it was not statistically significant. However, the risk of developing serous carcinoma was increased by 18% (RR=1.18, CI 0.89-1.56), and by 13% for invasive serous carcinoma (RR=1.13, CI 0.84-1.51). Additionally, 101 cases were categorized histologically as "other," including tumors that were self-reported, not validated and potentially may not have even been primary ovarian tumors. This would bias the risk estimate of talc use in ovarian cancer in this study toward the null by including cancers or other tumors potentially from other sites; in other words, non-specific cancer types may have been included that are not known to have an association with talc use. Another weakness of the study is that although the authors did evaluate the

effect of duration of use of genital talc on the risk of ovarian cancer, they did not evaluate frequency of use. Thus a woman who used talc for twenty years once a month would be treated the same as a woman who used it every day for twenty years. This will tend to understate or obscure the true risk of long term, frequent use. The study also was of an older age group (50-79) who were post-menopausal at time of enrollment, which adds selection bias.

Another study in which the effect of talc use on the risk of ovarian cancer is likely diluted or understated is the Sister Study, published by Gonzalez et al. in 2016. In this study, there was no reported association between perineal talc use and subsequent ovarian cancer. The study only enrolled women with a full or half-sister who had been diagnosed with breast cancer. BRCA1 and BRCA2 mutations are associated with a markedly increased risk of both breast and ovarian cancer, and in the Sister Study, women were not tested for this mutation. Most of the ovarian cancers associated with BRCA mutations are of the invasive serous subtype, the same subtype most strongly associated with talc use in prior studies. By not testing the women for the genetic mutation, the Sister Study analyzed a population of women with an increased risk of having a BRCA mutation (by having a first degree relative, or sister/half-sister, with breast cancer), a significant confounding factor that was not considered. Another limitation of this study is that the mean follow-up was 6.6 years, a very short period considering the generally long latency period of ovarian cancer. The Sister Study did find an increased risk in ovarian cancer in women who douched, providing evidence supporting the link between particulate route of access to the ovary/fallopian tube. The histologic subtype of the ovarian cancer was also not evaluated. Further, similar to the other cohort studies, the Gonzalez 2016 study failed to adequately capture both duration and frequency of talc exposure as participants were only asked if they used talc in the last 12 months.

XIII. META-ANALYSES REGARDING TALC USE AND OVARIAN CANCER:

Meta-analyses are an important tool that combines study results from multiple studies to develop a single result that has greater power to detect a more precise estimate of risk. Several meta-analyses have been published on the association between talc use and ovarian cancer, all showing an increased risk (Harlow and Cramer 1992, Gross and Berg 1995, Cramer and Harlow 1999, Huncharek 2003, Langseth 2008, Berge 2018, Penninkilampi 2018).

In 1992 Harlow and Cramer published combined results from six case-control studies of the association between talc use and ovarian cancer that were performed between 1982 and 1989. The association was statistically significant (OR=1.3, CI 1.1-1.6) (Harlow 1992). In 1995, Gross and Berg published a meta-analysis that included the six case-control studies evaluated in the 1992 Harlow and Cramer paper, plus three additional studies. This produced a statistically significant increased risk (OR=1.27, CI 1.09-1.48) (Gross 1995). Of note, this study was supported in part by Johnson and Johnson, raising the issue of funding bias.

Cramer published another meta-analysis in 1999 that included the nine studies in Gross and Berg's 1995 paper plus five additional ones performed through 1999. The overall risk of ovarian cancer in talc users was found to be increased at 36% (OR=1.36, CI 1.24-1.49) (Cramer 1999).

Huncharek et al. performed a meta-analysis in 2003 that added five new studies and included all of the previous studies except the 1983 Hartge and 1996 Shushan studies. The OR in this study was 1.33 (CI 1.16-1.45). Interestingly, the authors concluded that even with this statistically significant OR, the data "do not support the existence of a causal relationship" between talc use and ovarian cancer (Huncharek 2003). In a subsequent paper published by Huncharek et al., support from Johnson and Johnson and Luzanec America was acknowledged (Huncharek 2007), raising the issue of funding bias.

Langseth et al. published a comprehensive meta-analysis in 2008 of the risk of ovarian cancer associated with talc use. The combined OR was 1.35 (CI 1.26-1.46), and specifically 1.4 for population-based studies (CI 1.29-1.52), the less potentially biased type of study. Langseth et al. also noted that the risk of serous ovarian tumors in particular with talc use may be greater (Langseth 2008).

In 2016, Cramer published a retrospective case-control study that incorporated data from three enrollment phases (1992-1997, 1998-2002 and 2003-2008) and combined data from the Nurses' Health Study (Gates 2008) and data from participants in the Ovarian Cancer Association Consortium (OCAC, Terry 2013). The study found a statistically significant increased risk of invasive serous, invasive endometrioid and serous borderline ovarian tumors in women who were genital talc users, with the highest risk (OR=2.33 (CI 1.32-4.12) and OR=2.57 (CI 1.51-4.36) for pre- and postmenopausal women, respectively) with the greatest lifetime exposure, as defined by "talc-years," or number of applications per year multiplied by years of use. A dose-response was most prevalent for invasive serous carcinoma. This study is important as evidence supporting an association between talc and ovarian cancer as the authors analyzed case-control data collected over 16 years in 2,041 epithelial ovarian cancer cases and 2,100 age- and residence-matched controls. As the authors state, they "addressed issues related to definition of the exposure, bias and confounding, effect modification, histologic heterogeneity, and dose-response. Talc used regularly in the genital area was associated with a 33% increase in ovarian cancer risk overall." (Cramer 2016)

Berge et al. published another meta-analysis in 2018 that found a summary RR of 1.22 (CI 1.13-1.30). They found that the association between talc and ovarian cancer was stronger in case-control studies (RR 1.26, CI 1.17-1.35) than cohort studies (RR 1.02, CI 0.85-1.20). The limitations of the cohort studies are discussed above; limitations of case-control studies are recall bias and selection bias. Addressing the latter, Berge et al. found a higher summary risk estimate in hospital-based case-control studies compared to community-based case-control studies, but this difference was not statistically significant. Recall bias can be present in case-control studies, however, Berge et al. found the greatest association between genital talc use and serous carcinoma (RR 1.24, CI 1.15-

1.34). This would argue against recall bias, as participants would likely not know the categorization of epithelial ovarian tumors, nor the fact that invasive serous carcinoma has been shown to have the strongest association in the majority of studies.

Penninkilampi et al. published a meta-analysis in 2018 that found any perineal talc use was associated with an increased risk of ovarian cancer (OR 1.31, CI 1.24-1.39). They found a dose-response effect with greater than 3600 lifetime applications (OR 1.42, CI 1.25-1.61) compared to less than 3600 lifetime applications (OR 1.32, CI 1.15-1.50). Similar to the Berge 2018 study, an association was found in the case-control studies (OR 1.35, CI 1.27-1.43) but not in the cohort studies (OR 1.06, CI 0.90-1.25). However, Penninkilampi et al. did find an association in cohort studies between talc use and invasive serous carcinoma (OR 1.25, CI 1.01-1.55). (Penninkilampi 2018)

XIV. POOLED STUDY REGARDING TALC USE AND OVARIAN CANCER:

The meta-analyses discussed above summarize previously published data and thus have increased statistical power for a more precise estimate of effect on talc in ovarian cancer risk (Cohn 2003). However, the strength of meta-analyses depends on the quality of the previously published data analysis. In comparison, a pooled study analyzes primary data from different studies/researchers. The Terry 2013 study is a retrospective pooled study from eight population-based case-control studies from OCAC. One advantage of pooled studies is the ability to include a large sample size; Terry et al. included 8,525 cases of ovarian, fallopian tube or perineal cancer and 9,859 controls. Some of the included OCAC studies had previously reported on powder use (Chang 1997, Cramer 1999, Merritt 2008, Moorman 2009, and Rosenblatt 2011), and according to Terry et al., three of these provided data for the pooled 2013 analysis that had not been included in the previous publications. The other three studies had not previously published their genital powder data (Goodman 2008, Lo-Ciganic 2012, Pike 2004). The pooled analysis showed an OR for genital talc use and epithelial ovarian cancer of 1.24 (95% CI 1.15-1.33) after adjustment for age, oral contraceptive use, tubal ligation, BMI and race/ethnicity (Terry 2013). This is consistent with the majority of meta-analyses and individual studies.

A strength of a pooled study versus a meta-analysis is that pooled studies have increased standardization. As an example, the Terry 2013 study excluded participants that data was not available on regarding tubal ligation, oral contraceptive duration, parity or height and weight. This adjusts for study-specific differences in confounding factors. A weakness of pooled studies is that they are limited by the methods of original data collection; for example, Terry et al. state "Limitations of our pooled analysis include differences in the wording of questions about genital powder use between studies and the retrospective nature of the exposure ascertainment." As Blettner (1999) stated, "Pooling decreases the variation caused by random error (increasing the sample size) but does not eliminate any bias (systemic errors)." In the 2013 Terry et al. study, classification between cases and controls differed between studies, as the women who were classified as genital powder users varied from "ever" use, "ever regular" use, to powder use for at least one year. However, Terry et al. conclude that if anything, this led to an underestimate of the true association for any given

study “[due to the fact that] exposure definitions are the same for cases and controls within each study, misclassification of genital powder exposure due to the question wording would be nondifferential....” (Terry 2013).

XV. ASBESTOS, TALCUM POWDER PRODUCTS, AND OVARIAN CANCER:

I have seen evidence that talcum powder products manufactured by Johnson & Johnson (J&J Baby Powder and Shower to Shower) contained and continue to contain asbestos, talc containing asbestiform fibers (e.g. talc occurring in a fibrous habit) heavy metals (such as cobalt, chromium, nickel) and fragrance chemicals (Longo et al. 2017 and 2018, Blount 1991, Blount Deposition 2018, Hopkins Deposition and Exhibit 2018, Pier Deposition and Exhibit 2018). Other than cobalt, which has been identified as a “possible” carcinogen, all of these constituents have been identified as known carcinogens by IARC (IARC 2012). It should be noted that National Institute for Occupational Safety and Health (NIOSH) has determined that “there is no safe level of asbestos exposure for any type of asbestos fiber” (NIOSH 1980). As part of my review and consideration of the evidence I have also reviewed Dr. Michael Crowley’s opinion that “fragrance chemicals in Johnson & Johnson talcum powder products contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products.” The presence of these constituents as part of the talcum powder product provides additional evidence of biological plausibility for talcum powder products to cause ovarian cancer.

Asbestos is a silicate mineral in polyfilamentous bundles. Other silicate minerals exist, such as talc, but asbestos is classified by its flexible fibers with small diameter and large length. The forms of asbestos are serpentine silicates (“sheet silicates”) such as chrysotile, and amphibole silicates (“chain silicates”) such as crocidolite, amosite, anthophyllite, actinolite, and tremolite (IARC Monograph). The carcinogenic properties of asbestos fibers depend on the length of the fiber (Stanton 1972) and its chemical composition, structure, and cell environment (Mossman 1998, Robledo 1999, IARC Monograph). Asbestos fiber surface reactivity with free radical generation has also been accepted as a mechanism of carcinogenesis (IARC Monograph). Asbestos-derived free radicals can lead to a variety of effects on cells including lipid peroxidation, DNA oxidation, TNF release, cell apoptosis, and increased uptake of asbestos fibers (Mossman 1983, Hobson 1990, Ghio 1998, Churg 1998, Gulumian 1999, Aust 1999, Upadhyay 2003, IARC Monograph). Asbestos fibers may directly cause the generation of ROS (IOM 2006) and indirectly cause ROS by inducing inflammation and macrophage activation (IARC Monograph).

It has long been generally accepted that asbestos exposure causes mesothelioma and lung cancer (Dement 1994, deKlerk 1996, Berry 2000). Approximately 125 million people around the world have been exposed to asbestos in work environments, and at least 90,000 people die each year from asbestos-related lung cancer, mesothelioma, or asbestosis (Burki 2009). The relationship between asbestos exposure and ovarian cancer had been less studied; however, in 2009, the IARC Monograph Working Group concluded that there is sufficient evidence to show that asbestos exposure can cause ovarian cancer (Straif 2009, IARC Monograph).

In the late 1960's, a suggested link between talc and ovarian cancer was made for the following reasons: first, talc powders were shown to contain asbestos (Cralley 1968); second, intraperitoneally placed asbestos in animals induced a proliferation of the ovarian mesothelial lining from one layer to multiple layers (Graham 1967). Of note, it was tremolite asbestos that was used by Graham, the same type of amphibole asbestos that is found in asbestos-contaminated talc. It is important to note that similar to talc being found on the ovarian surfaces of perineal talc users, asbestos fibers have been found in women whose household contacts worked with asbestos and in Norwegian paper and pulp workers (Heller 1996, Langseth 2007).

In 1972, Newhouse et al. published a study of the mortality of female asbestos workers and found at least 4 deaths due to ovarian cancer compared to an expected number of 0.6. During histological review of some of the pathology samples from these workers, there was evidence that another two deaths that had been registered as due to carcinomatosis were likely caused by ovarian cancer (Newhouse 1972).

Ten years later in 1982, Wignall et al. published a study that followed 535 women who were assembly workers that had direct crocidolite exposure during the manufacturing of military gas masks. The authors found 2 deaths due to ovarian cancer in women that were employed at the facility for less than 1 year, with a standardized mortality rate (SMR) of 1.77. Two ovarian cancer deaths occurred in women with a 1 year history of employment at the facility (SMR=2.11) and one ovarian cancer death in a woman with a 3 year history of employment (SMR=1.05). The authors noted that the expected number of deaths is low, making stable estimates of SMR difficult. However, the authors conclude that the "excess of deaths from carcinoma of the ovary was unexpected at the start of the study but appears to be related directly to exposure to asbestos" (Wignall 1982).

Also published in 1982 was a study by Acheson et al. that evaluated two groups of women exposed to asbestos who assembled gas masks in two separate facilities: 570 women at Blackburn (civilian respirators that contained chrysotile) and 757 women at Leyland (military respirators containing crocidolite). The study found a SMR in the crocidolite group for ovarian cancer of 2.75 (CI 1.42-4.81) and a SMR of 1.48 (CI 0.48-3.44) for the chrysotile group. The authors noted that the risk of ovarian cancer increased over time for up to 40 years post exposure (Acheson 1982).

A 1994 study by Rosler et al. examined mortality from ovarian cancer in a cohort of 616 women in Germany who had been occupationally exposed to asbestos. Although about 95% of asbestos used in Germany was chrysotile, the authors noted that they could not exclude a mixture containing crocidolite. Two deaths from ovarian cancer were observed, compared to an expected 1.8 (SMR 1.09, CI 0.13-3.95). (Rosler 1994).

In 1999, Germani et al. published a study of ovarian cancer mortality in 631 women workers in Italy who had been compensated for asbestosis. They found a total of nine ovarian cancer deaths (SMR 4.77, CI 2.18-9.04) which included four deaths in a subset of asbestos-textile workers (SMR 5.26, CI 1.43-13.47) and five deaths in the subset of asbestos cement workers (SMR 5.40, CI 1.75-12.61). (Germani 1999).

Also in 1999, Vasama-Neovonen et al. published a case-control study of ovarian cancer and occupational exposure in Finland. The Standardized Incidence Ratio (SIR) was 1.30 (CI 0.9-1.80) between ovarian cancer and “medium/high levels of asbestos,” and the SIR was 1.1 (CI 0.8-1.3) for “low levels of asbestos.” The SIR is obtained by dividing the observed number of cases of cancer by the expected number of cases in the general population. The type of asbestos fiber was not noted (Vasama-Neovonen 1999).

Again in 1999, Langseth et al. published a study of 4247 workers employed for at least one year between 1920 and 1993 in the Norwegian pulp and paper industry. 85% of them were paper or administration workers. The follow-up period for cancer was from 1953-1993. An excess risk of ovarian cancer was found (SIR = 1.50, CI 1.07-2.09). The SIR was highest among those younger than 55 years, and mostly among those working in paper departments. The type of asbestos fiber was not specified (Langseth 1999). Langseth et al. published a follow-up case-control study in 2004 that examined the association between asbestos exposure and ovarian cancer in this same cohort of female pulp and paper workers in Norway that had been found to have excess morbidity from ovarian cancer. In the case-control study, the odds ratio for occupational exposure to asbestos based on 46 cases of ovarian cancer was 2.02 (CI 0.72-5.66), although this was not statistically significant (Langseth 2004).

In 2000, Berry et al. published a study that evaluated the mortality of a cohort of over 5000 London asbestos factory workers, both men and women, who were followed for over 30 years since first asbestos exposure. The study classified exposure by degree (low, moderate and severe) and duration (2 years or less or more than 2 years). They assessed mortality by comparing the number of cohort deaths with the number of expected deaths in England and Wales based on sex, age and period. The study found that there was a significant increase of ovarian cancer in women with severe exposure for more than 2 years (SMR of 5.35) and an overall SMR for all exposure lengths of 2.53 (CI 1.16-4.8) (Berry 2000).

In 2005, Pira et al. published a cohort study of 1077 women with at least a one month history of employment between 1946 and 1984 at an asbestos-textile factory in Italy. A variety of asbestos types were used in this facility, including crocidolite. They followed up with the cohort in 1996. There were five deaths due to ovarian cancer with an overall SMR of 2.61 (CI 0.85-6.09), but there was a SMR of 5.73 for women with longer employment histories at the facility (greater than or equal to 10 years of employment). Among women with greater than or equal to 35 years since first employment exposure, the SMR was 5.37 (Pira 2005).

Also in 2005, Wilczynska et al. published a study of 1470 Polish asbestos cement factory workers with a follow-up period from 1945 to 1999 and a SMR of ovarian cancer among workers of 3.76 (CI 1.38-8.18). The type of asbestos fiber was not specified (Wilczynska 2005).

McDonald et al. published a study in 2006 that followed 567 people, mostly women, who had assembled gas masks in the Nottingham factory between 1940 and 1944 and showed

a SMR for ovarian cancer of 1.2 (CI 0.6-2.2). Gas masks assembled at this facility had filter pads that contained 20% crocidolite. As an aside, this study found that the first deaths due to mesothelioma happened a little more than 20 years after exposure, which is consistent with most other studies (McDonald 2006) and highlights the lengthy time interval between exposure and presentation of disease in asbestos-related mesothelioma.

In 2008 Reid et al. published a study of 2552 women and girls who lived in a Western Australia mining town between 1943 and 1992 where crocidolite asbestos was mined. They were not directly involved in mining but there was extensive environmental contamination of the town. They found a SMR for ovarian cancer of 1.52 (Reid 2008).

Reid et al. published a study in 2009 that followed the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos and added 416 women to the study that had worked in the Wittenoom crocidolite asbestos mines and mills. For the latter group, there wasn't an increased rate of ovarian cancer (SIR of 0.49, CI 0.01-2.74), but the authors noted that the "female Australian Blue Asbestos workers at Wittenoom mostly worked in the company offices, shop, and hotel. Their occupational exposure was unlikely to have been as high as that reported for women in the earlier cohorts, which may explain why no excess risk for ovarian cancer was observed" (Reid 2009).

Pukkala et al. published a study in 2009 on the incidence of ovarian cancer in women employed in various occupations in Denmark, Finland, Iceland, Norway and Sweden. One of the groups examined were plumbers, who are known to have occupational exposure to asbestos. Four ovarian cancers were found in this group of plumbers, with a Standardized Incidence Rate (SIR) of 3.33 (CI 0.91-8.52). Fiber type was not specified (Pukkala 2009).

Magnani et al. and Bertolotti et al. published studies in 2008 that followed the same cohort of former asbestos-cement workers who were employed at a facility in Casale Montferrato, Italy. A mix of crocidolite and chrysotile asbestos was used at this factory. They observed nine ovarian cancer deaths versus 4 expected (SMR of 2.27). In women who had 30 or more years of exposure, the SMR was 2.97 (Magnani 2008, Bertolotti 2008). Ferrante et al. published a study in 2007 that examined cancer mortality in the household contacts of men who worked at this facility; among women with exposure due to household contacts, there were 11 ovarian cancer deaths versus an expected 7.7, or SMR of 1.42 (CI 0.71-2.54). (Ferrante 2007).

I am aware of two meta-analyses, both published in 2011, that evaluated a link between asbestos and ovarian cancer. The first was published in 2011 by Reid et al. and analyzed fourteen cohort and two case-control studies of women with exposure to asbestos in their work environment. The majority of the cohort cases they evaluated are detailed above. The authors added a 2002 paper by Szeszenia-Dabrowska et al. that studied Polish women diagnosed with asbestosis and a 2004 paper by Mamo et al. that studied Turin asbestos textile factory workers (Szeszenia-Dabrowska 2002, Mamo 2004). The two case-control studies they evaluated were a 1992 study of Johns Hopkins patients by Rosenblatt et al. and a 2004 study

of Norwegian pulp and paper workers by Langseth et al., the same group of workers previously described above. Reid et al. concluded that although women “thought to have ovarian cancer” (not all cases of ovarian cancer were histologically reviewed and confirmed) had an increased rate if exposed to asbestos, the overall numbers were still small and further study was warranted as one misclassification could skew the data (Reid 2011).

The authors of the second 2011 meta-analysis, Camargo et al., included 18 studies. They did not include the 1992 Rosenblatt et al. study or the 2004 Langseth et al. study but added six others: a 1986 study of cement workers in the U.K. by Gardner et al., a 1989 study of friction material workers in the U.K. by Newhouse et al., a 2007 study of textile workers in the U.S. by Hein et al., a 2009 study of textile workers in the U.S. by Loomis et al., and two other 2009 studies by Harding et al. and Clin et al. The authors of this second meta-analysis came to a stronger conclusion that the findings were consistent with an association between asbestos exposure and an increased risk of ovarian cancer (Camargo 2011).

Considering the consistency of these studies, the Bradford Hill viewpoints (strength of association, consistency, biological plausibility, etc.) and the well-known carcinogenic properties of asbestos, it is my opinion to a reasonable degree of scientific certainty that asbestos exposure can cause ovarian cancer. Even disregarding the evidence that cosmetic talc is contaminated with asbestos, it is my opinion that talc is causally associated with ovarian cancer. However, to the extent that talcum powder products contain even small amounts of asbestos, the evidence of causation is even more compelling.

XVI. BRADFORD HILL ANALYSIS:

In 1965, Sir Austin Bradford Hill proposed nine viewpoints of a causal relationship: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment and analogy (Hill 1965). It is important to remember, however, as discussed at the beginning of this report, that Hill himself noted that none of these viewpoints of association – including the existence of a statistically significant relationship – is either necessary or sufficient to show causation. There are no “hard-and-fast rules”. Rather, the totality of the evidence must be weighed and considered. With that important command in mind, let us examine the evidence.

1. Strength of association:

Strength of association is often measured by the magnitude of the relative risk (CDC). All meta-analyses and pooled analyses have found a statistically significant increased risk of ovarian cancer in perineal talc users, with relative risks falling between 1 and 2. This is consistent with a causal relationship. Strength of association is higher for asbestos. There are a number of examples of causal relationships where the relative risk is less than 2.0 (e.g., second hand smoke and lung cancer, oral contraceptive use and breast cancer, radon exposure and lung cancer). It also is worth noting that small or moderate effects on the benefit side can have important clinical significance. For example, aspirin has been deemed “causal” of cardiovascular event reduction, based on multiple studies that reported a benefit between 20-30% reduction in cardiovascular events. The strength of this association, especially combined

with the consistency, weigh in favor of a cause-and-effect relationship between talc and ovarian cancer.

2. Consistency:

The statistically significant increased risk of ovarian cancer with talc use has been consistent in size across multiple studies, different populations, different investigators, multiple countries and over time. Hill stressed the importance of repetitive findings; no single study can prove or disprove causation due to possible inherent internal validity issues. The consistency of the increased risk of ovarian cancer (and in particular invasive serous carcinoma) with talc use found in numerous studies, in different countries, and after adjustments for confounding factors cannot be disregarded. There also is consistent evidence of an association between asbestos and ovarian cancer. This was a very important factor in my analysis.

3. Specificity:

Hill suggested that associations are more likely to be causal when they are specific, in other words, a particular substance causes a single disease. However, in the half-century experience has shown that this aspect of causation is not particularly important in the context of cancer. Few examples of specificity are found when it comes to cancer. Smoking is generally accepted to be a cause of lung cancer, yet smoking is also associated with COPD, heart disease, stroke, and asthma, amongst other diseases. In multiple studies, talc has been shown to be associated with epithelial ovarian cancer, with invasive serous ovarian cancer showing the strongest association. Asbestos is generally accepted to cause mesothelioma, lung cancer, and ovarian cancer. Asbestos is also generally accepted to cause asbestosis/pulmonary fibrosis, pleural inflammation and thickening. This was a less important factor in my analysis.

4. Temporality:

Exposure to a substance must precede onset of disease for it to be causal. The above-described case-control and cohort studies had the objective of assessing talc exposure that preceded the onset of disease. In cohort studies, the exposure data was obtained before any women were diagnosed with ovarian cancer. In the case-control studies, women with ovarian cancer reported exposures prior to their diagnosis and controls reported exposures in the same time frame. In many studies the exposures went back several decades, providing even more assurance that the temporality requirement is met. This was an important factor in my analysis.

5. Biological gradient:

A biologic gradient, or dose-response, refers to an increased exposure corresponding to an increased risk. In the case of talc exposure, dose-response would ideally include both frequency of use and duration of use, or “application years” (total lifetime applications) similar to “pack-years” used in the setting of smoking. However, application-years is much more difficult to assess than pack-years, since one cannot easily quantify the amount of talc

used during each perineal application (unlike in smoking, where one can easily count the number of cigarettes smoked to calculate pack-years). Yet, when studies have evaluated duration and frequency of perineal talc use, most have found an increased risk of ovarian cancer with increased exposure (Harlow 1992, Cramer 1999, Mills 2004, Merritt 2008, Wu 2009, Terry 2013, Penninkilampi 2018). In the case of asbestos and mesothelioma, a study published by Plato et al. in 2018 found “a significant, dose–response relationship between maximum intensity asbestos exposure and mesothelioma of the pleura and cumulative asbestos exposure with 30-, 40-, and 50-years lag time. Cumulative exposure to asbestos, even at low levels, entailed an increased risk of mesothelioma of the pleura, indicating that even short periods with cumulative doses <1.78 f-y/ml can increase the risk of mesothelioma. Time since first exposure did not show any sufficient dose–response relationship in the longest lag period (>50 years).” (Plato 2018)

While there is evidence of a dose response, this data is more equivocal because of the challenge in measuring and comparing the extent of talcum powder usage. The evidence of biological gradient for talcum powder products is therefore very difficult to study. The evidence of biological gradient supports cause and effect, but for the reasons noted, it is limited by difficulties in the measurement of exposure. This was an important factor in my analysis.

6. Plausibility:

In this context, plausibility means that an association can be explained by and is consistent with existing scientific knowledge and, in particular, that there is a biologically plausible explanation for the exposure (to talc) as a cause of ovarian cancer. Thus, plausibility is dependent upon the current state of scientific knowledge regarding a mechanism of disease. Hill noted plausibility is helpful but limited by current knowledge.

There is evidence that validates the biological plausibility of talc-related ovarian cancer. It is generally accepted that inflammation plays a role in carcinogenesis. Pelvic inflammatory disease and endometriosis are known risk factors for ovarian cancer, and they cause the release of inflammatory mediators. Talc is known to produce an inflammatory reaction, and is in fact used in clinical practice to induce inflammation in the pleura to treat patients with pneumothorax and pleural effusions. It has also been demonstrated that particles, including talc, can migrate proximally through the female genital tract and gain access to the perineum, ovaries, and fallopian tubes. Thus, it is plausible that talc can reach the ovaries and fallopian tubes and cause a proinflammatory reaction, including induction of cytokines and ROS that play a role in the onset of ovarian cancer. Other plausible mechanisms include a down-regulated immune response to MUC1, causing an immune tolerance of a MUC1-expressing cancer, and talc-induced macrophage TNF- α expression and subsequent ovarian tumorigenesis. The 2008 Gates study showed an association of talc and ovarian cancer in women with the GSTT1-null genotype (p-interaction=0.03), particularly in combination with the GSTM1-present genotype (p-interaction=0.03). It is thus plausible that women with a GSTT1-null phenotype are unable to eliminate talc as efficiently and are at increased risk of ovarian cancer. It is also highly plausible that asbestos in asbestos-tainted talc also releases cytokines and mutagenic ROS from inflammatory cells.

In the case of asbestos, fiber surface reactivity with free radical generation has been accepted as a mechanism of carcinogenesis (IARC Monograph). Asbestos-derived free radicals can lead to a variety of effects on cells including lipid peroxidation, DNA oxidation, TNF release, cell apoptosis, and increased uptake of asbestos fibers (Mossman 1983, Hobson 1990, Ghio 1998, Churg 1998, Gulumian 1999, Aust 1999, Upadhyay 2003, IARC Monograph). Asbestos fibers may directly cause the generation of ROS (IOM 2006) and indirectly cause ROS by inducing inflammation and macrophage activation (IARC Monograph). As noted above, the carcinogenicity of the other constituents of talc (cobalt, chromium, nickel, and fragrance ingredients) adds strength to biologic plausibility.

This biologic evidence, provides a biologically plausible explanation for the increased risk seen in the epidemiologic studies and is therefore a very strong factor in favor of a cause and effect relationship.

7. Coherence:

Coherence in this context means coherence between epidemiological and generally accepted knowledge of the disease in question. Numerous studies addressing talc use and ovarian cancer have indicated talc use increases ovarian cancer risk consistently. The coherence of the epidemiological evidence linking a risk of ovarian cancer with talc use, in tandem with biologically plausible mechanistic evidence discussed above, is striking and weighs heavily in support of causation.

8. Experiment:

Hill suggested that evidence drawn from experimental manipulation, particularly epidemiologic studies in which disease risk declines following an intervention or cessation of exposure, may lead to the strongest support for causal association. No studies exist that follow women after cessation of genital powder use and assess them specifically for a change in risk of ovarian cancer. The challenge of such a study is that it has been shown that talc-associated ovarian cancer takes years or decades before onset of disease. However, the Australian study performed by The Survey of Women's Health Study Group published in 1997 found that the risk of ovarian cancer was highest among women who were talc users and had not undergone surgical sterilization (RR=1.3, CI 1.1-1.6). (Green 1997). This indicates that tubal ligation or hysterectomy, by impeding the proximal migration of talc into the perineum to the ovaries and fallopian tubes, decreases the risk of talc-associated ovarian cancer, lending support to Hill's experiment aspect in the context of talc and ovarian cancer.

There are experimental studies in the literature that support a causal relationship between talc and ovarian cancer. Examples include studies that show increases in inflammatory markers following talc exposure (Allaire 1989, Genofre 2009, Arellano-Orden 2013). There is also evidence that talc causes neoplastic transformation in ovarian cells (Buz'Zard 2007) and that talc induces genotoxicity in mesothelial cells (Shukla 2009). Additionally, there is evidence that talc induces macrophage TNF- α expression (Cheng 2000), and macrophages that express TNF- α have been shown to promote ovarian tumorigenesis

(Hagemann 2006). Of note, invasive serous carcinomas commonly have p53 mutations and TNF- α induced chromosomal mutations have been shown to occur mostly in cells with p53 aberrations (Yan 2006).

It has long been generally accepted that asbestos exposure causes mesothelioma, ovarian cancer, and lung cancer (Dement 1994, deKlerk 1996, Berry 2000, IARC 2012). The experimental evidence was very important to my analysis.

9. Analogy:

Comparisons of similar associations can be used to determine plausibility. Hill suggested that when there is strong evidence of a causal relationship between a particular agent and a specific disease, researchers should be more accepting of weaker evidence that a similar agent may cause a similar disease. Analogy under the Bradford Hill viewpoints has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way (Susser 1991). In the case of talc and ovarian cancer, one can use the analogy of asbestos and mesothelioma. Both talc and asbestos are silicates, and asbestos causes an inflammatory and fibrosing reaction within the pleura, which is generally accepted to be the primary cause of mesothelioma years later. It is the inflammatory and fibrosing reaction caused by talc that has led to its common use in the treatment of pneumothorax and pleural effusions by injection into the pleural cavity. Similarly, in the case of asbestos, fiber surface reactivity with free radical generation has been accepted as a mechanism of carcinogenesis (IARC Monograph). The analogy evidence was somewhat important in my analysis.

XVII. CONCLUSION:

Based upon the totality of the evidence and consideration of the Bradford Hill viewpoints, which includes the high consistency and replication of the findings in the epidemiological studies, pathological, biological, and mechanistic evidence, it is my opinion, which I hold to a reasonable degree of scientific and medical certainty, that genital talcum powder exposure can cause ovarian cancer.

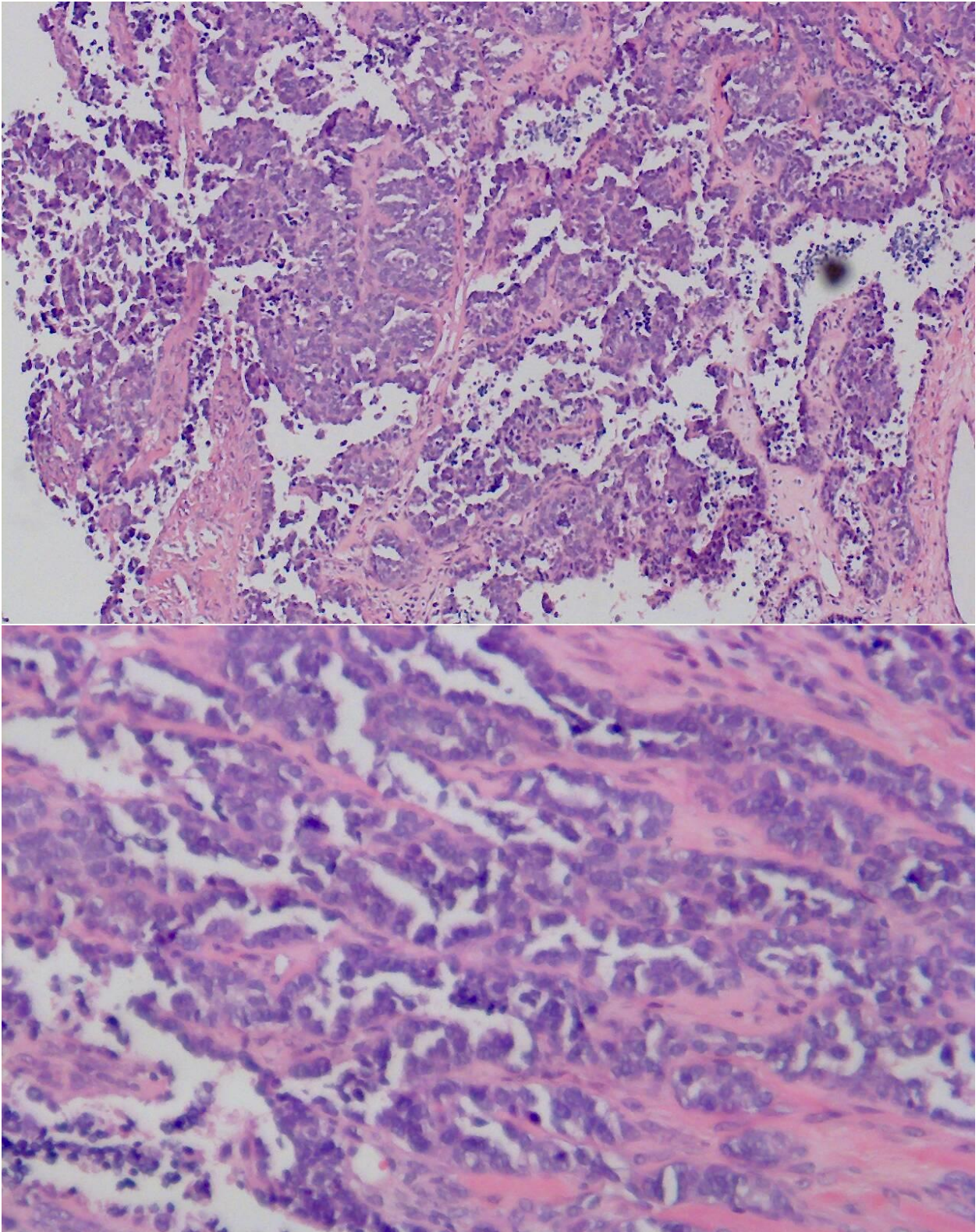


Figure 1. Ovarian invasive serous carcinoma.

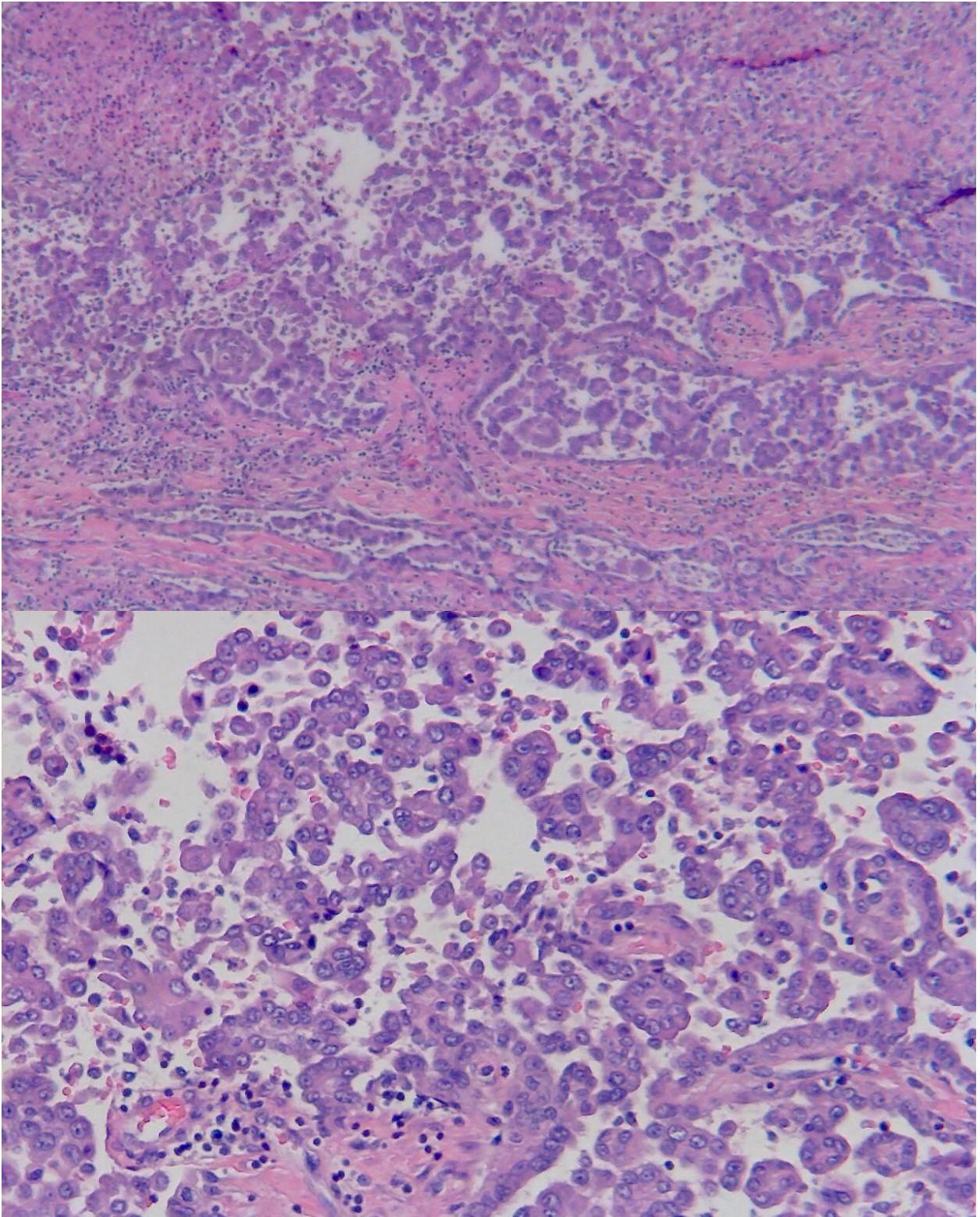


Figure 2. Mesothelioma. Notice the morphologic similarities to ovarian serous carcinoma (Fig 1).

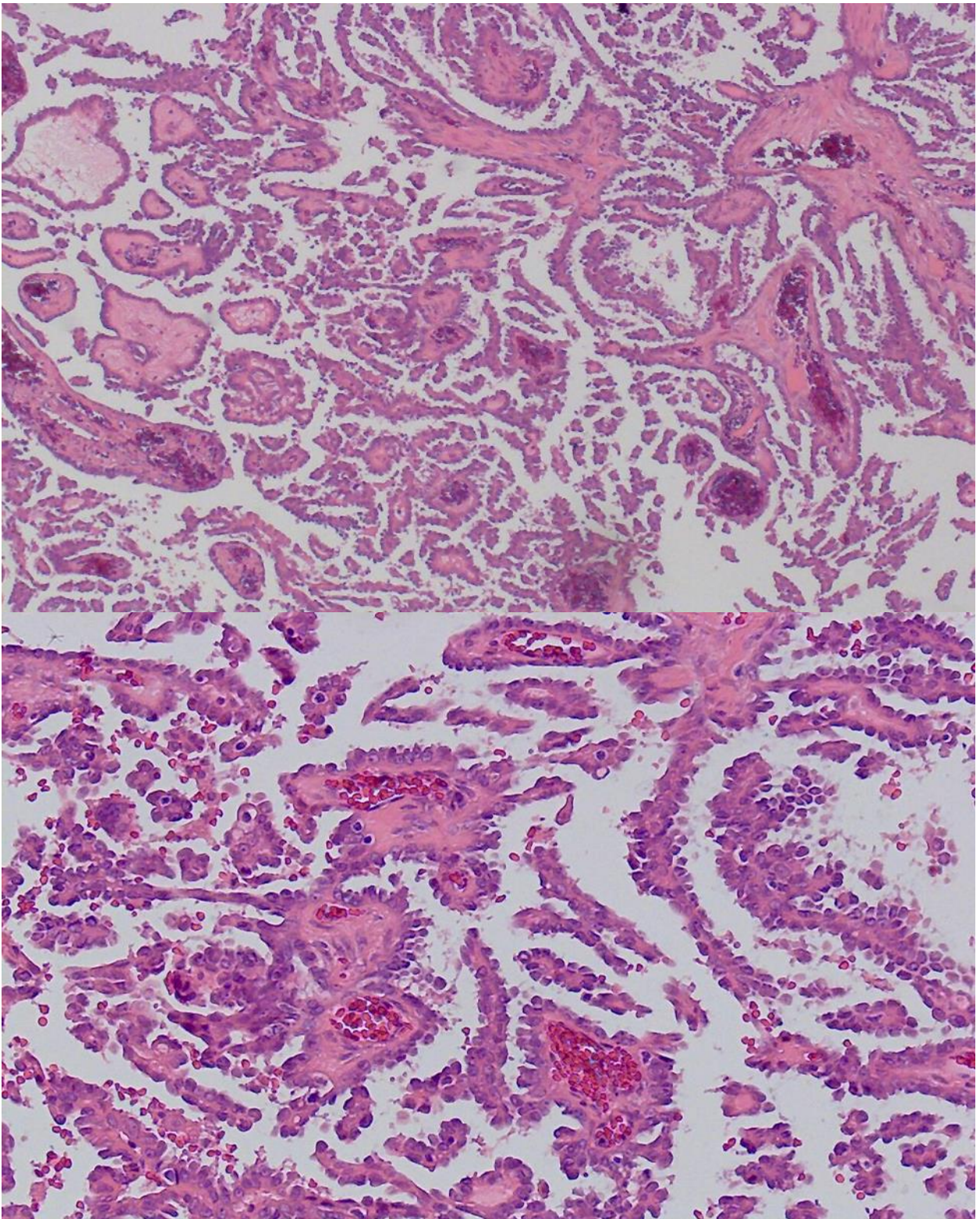


Figure 3. Ovarian serous borderline tumor.

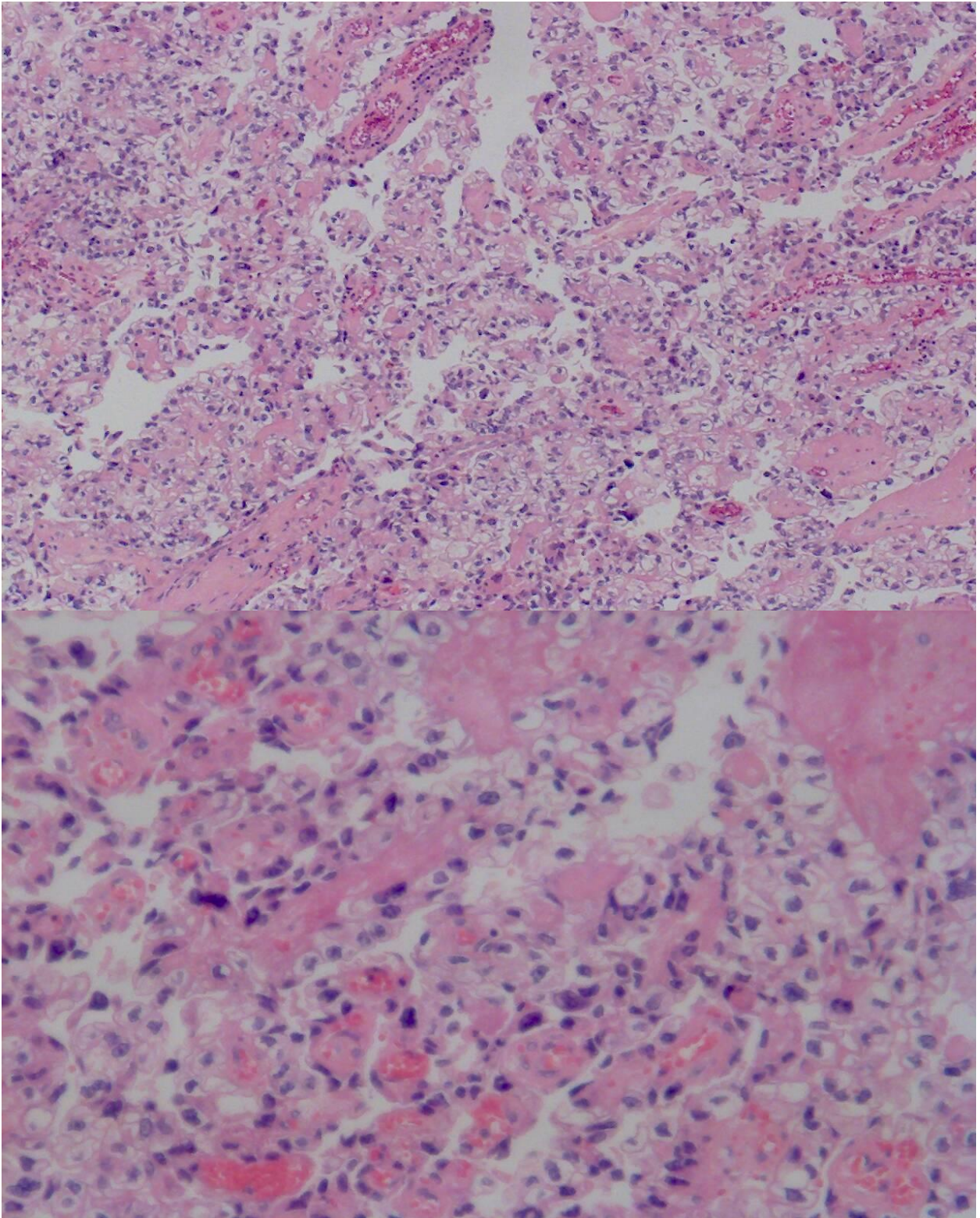


Figure 4. Ovarian clear cell carcinoma.

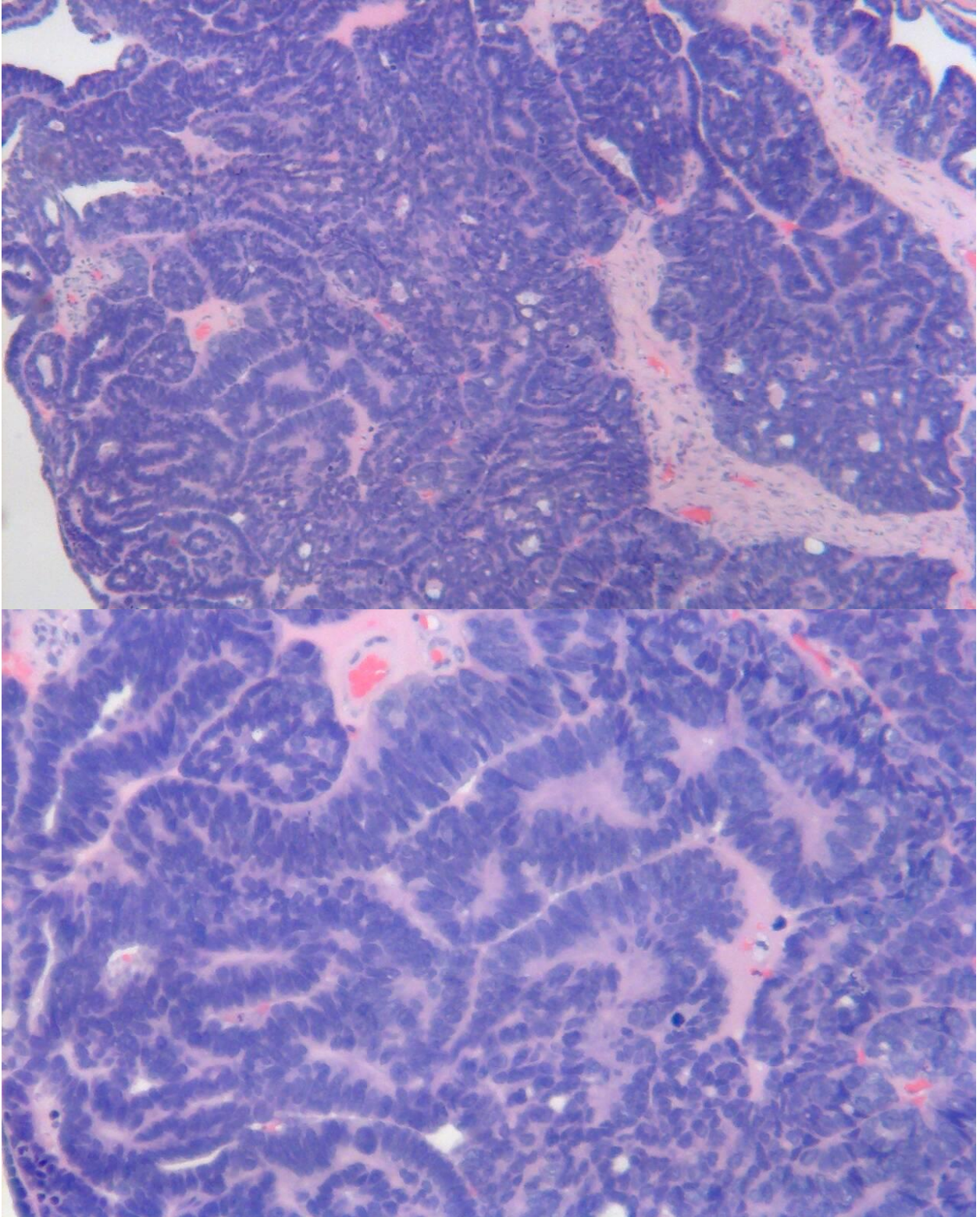


Figure 5. Ovarian endometrioid carcinoma.

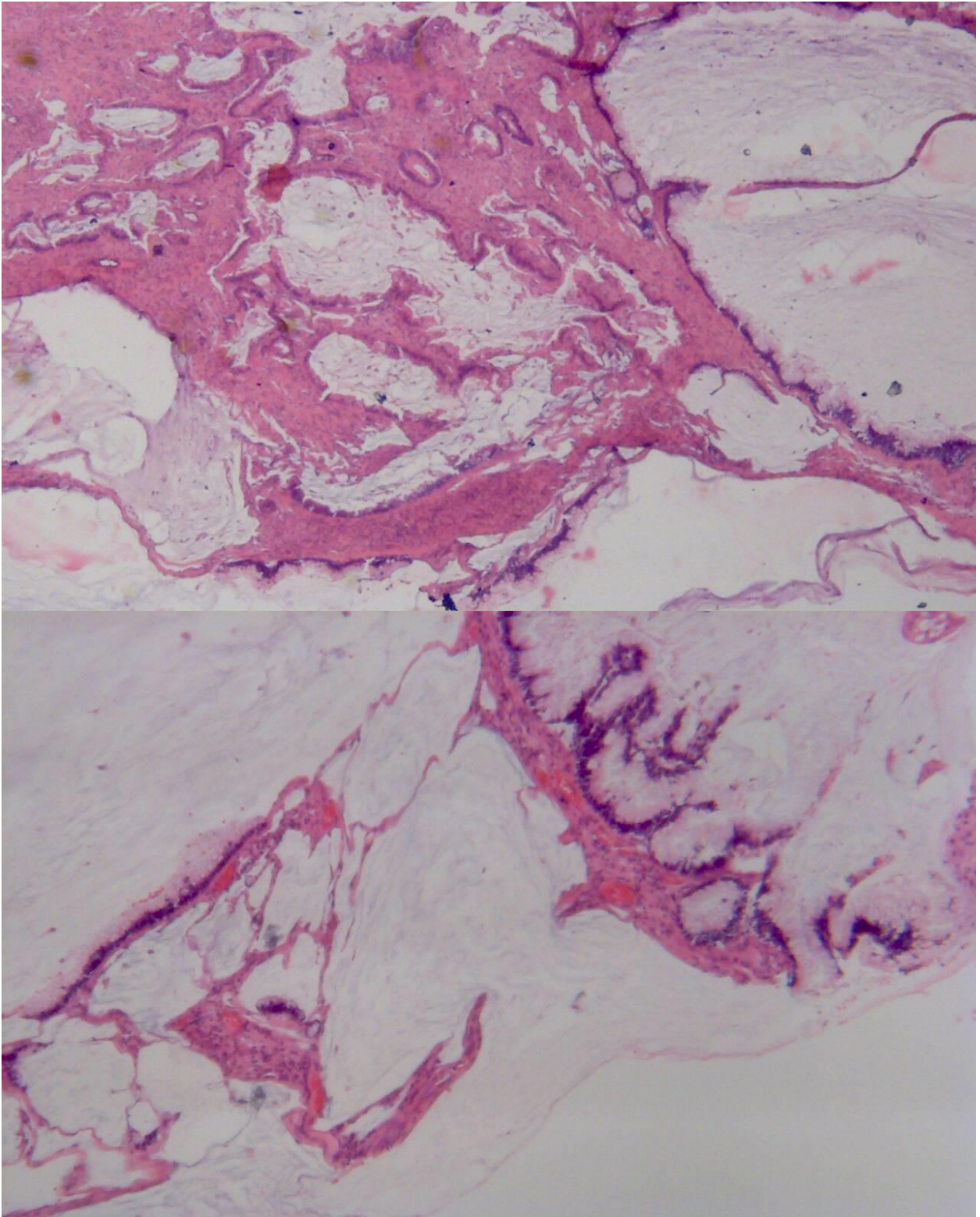


Figure 6. Ovarian mucinous carcinoma.

EXHIBIT A

CURRICULUM VITAE

Date prepared: January 2018

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Place of Birth: Norwalk, CT

Education:

1995	B.A.	Skidmore College Cum laude
2001	M.D.	The Ohio State University College of Medicine

Postdoctoral Training:

2001-2005	Resident	Pathology, AP/CP	Massachusetts General Hospital
2005-2007	Fellow	Robert E. Scully Fellow	Massachusetts General Hospital
		Cytopathology, Gynecologic and Perinatal Pathology	

Academic Appointments:

2001-2005	Clinical Instructor	Pathology	Harvard Medical School
2005-2007	Graduate Assistant	Pathology	Harvard Medical School
2007-2011	Instructor	Pathology	Harvard Medical School

Appointments at Hospitals/Affiliated Institutions

2007-2011	Staff Pathologist	Pathology	Beth Israel Deaconess
2007-2011	Staff Pathologist	Pathology	Beth Israel Deaconess-Needham
2011-Present	Staff Pathologist	Pathology	North Shore Medical Center
2011-Present	Staff Pathologist	Pathology	Newton-Wellesley Hospital
2011-Present	Clinical Affiliate	Pathology	Massachusetts General Hospital

Major Administrative Responsibilities:

2005	Chief Resident, Anatomic Pathology	Massachusetts General Hospital
2007-2011	Course Director, PA501.5 Elective	Harvard Medical School
2010-2011	Associate Director, Cytopathology Fellowship	BIDMC/Harvard
2012-2013	Hematology Laboratory Director	NSMC/Partners
2013-Present	Autopsy Director, North Shore Medical Center	NSMC/Partners

Major Committee Assignments:

2005-2007	Cytopathology	Junior Member	College of American Pathologists
2005	Path Residency Training Committee	Member	Massachusetts General Hospital
2005	Anatomic Path Quality Assurance	Member	Massachusetts General Hospital
2005	Anatomic Path Steering Committee	Member	Massachusetts General Hospital
2008-2011	Path Resident Selection Committee	Member	Beth Israel Deaconess
2009-2011	Path Residency Planning Committee	Member	Beth Israel Deaconess
2010	Pathology Scheduling Committee	Member	Beth Israel Deaconess
2010-2011	Anatomic Path Quality Assurance	Member	Beth Israel Deaconess

Professional Societies:

1997 – 2001	American Medical Student Association	Member
2001 – Present	Massachusetts Medical Society	Member
2003 – Present	United States and Canadian Academy of Pathology	Member
2005 - Present	College of American Pathologists	Member

Awards and Honors:

1994	Charlotte W. Fahey Prize in Chemistry, Skidmore College
1994	Skidmore College Periclean Honor Society
1995	Phi Beta Kappa, Skidmore College
1995	Cum Laude with Department Honors, Skidmore College
2000	Honors in Pediatric Hematology and Oncology 4th Year Clerkship
2000	Letter of Commendation, Surgery Third Year Clerkship
2000	Letter of Commendation, Neurology Third Year Clerkship
2001	Honors in Anatomic and Clinical Pathology Fourth Year Elective
2001	Honors in Individual Studies in Pathology Fourth Year Elective
2016	Partners in Excellence Team Award

Teaching of Students:

Harvard Medical School Courses:

2007-2009	Respiratory Pathophysiology
2 nd Year Medical Students	Lab Instructor Three 2 hour sessions, one week

2007-2009	Cardiovascular Pathophysiology	
2 nd Year Medical Students	Lab Instructor	Three 2 hour sessions, one week
2007-2011	Core Surgery Clerkship	
3 rd Year Medical Students	Pathology Coordinator	One hour lecture/3 months
2009-2011	Principal Clinical Experience	
3 rd Year Medical Students	Mentor	Two hour session per week
2009-2011	Principal Clinical Experience – Pathology Elective	
3 rd Year Medical Students	Mentor	Minimum 2 hour session/month

Formal Teaching of Residents:

2007	Respiratory Cytology	
All pathology residents	Beth Israel Deaconess	One hour lecture
2007-2011	Respiratory Cytology	Quarterly 1 hr microscope session
Pathology residents rotating through Cytology		
2008-2011	Fine Needle Aspiration Techniques	
All pathology residents	Beth Israel Deaconess	One hour lecture
2008-2011	Histologic and Cytologic Correlation of Cervical Lesions	
All pathology residents	Beth Israel Deaconess	One hour lecture

Clinical Supervisory and Training Responsibilities:

2007-2011 Core Surgery Clerkship, Pathology Elective BIDMC 2 students/month

Local Invited Presentations:

2005 Cytology/Histology Correlation Clinical Pathology Technician Lecture Series
Department of Pathology, Massachusetts General Hospital

2008 Respiratory Cytology Cytopathology Lecture Series
Department of Pathology, Brigham and Women's Hospital

Current Licensure and Certification:

2005	Full License, Massachusetts
2008	Board certified, Anatomic and Clinical Pathology
2008	Board certified, Cytopathology

Practice Activities:

Surgical Pathology, Cytopathology, Autopsy	North Shore Medical Center
Surgical Pathology, Cytopathology	MGH Ambulatory Care Center
Cytopathology	Massachusetts General Hospital
Clinical Pathology	Newton-Wellesley Hospital

Peer-Reviewed Publications:

Narasimhan V, Malboueuf B, **Hodil SE**. Temperature Induced Interstrand Crosslinks in Cisplatin-DNA Adducts Detected by Electrophoresis and UV Spectrophotometer. *Biochem Mol Biol Int*. 1995;37:843-851.

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Chan MP, Hecht JL, **Kane SE**. Clinicopathologic Correlation of Fetal Vessel Thrombosis in Mono- and Dichorionic Twin Placentas. *J Perinatol*. 2010 Oct; 30(10):660-4.

Kane SE, Hecht JL. Endometrial Intraepithelial Neoplasia Terminology in Practice: 4-Year Experience at a Single Institution. *Int J Gynecol Cancer*. 2012 Mar;31(2):160-165.

Haspel RA, Bhargava P, Gilmore H, **Kane SE**, Powers A, Sepehr A, Weinstein A, Schwartzstein R, Roberts D. Successful Implementation of a Longitudinal, Intergrated Pathology Curriculum During the Third Year of Medical School. *Arch Pathol Lab Med*. 2012 Nov;136(11):1430-6.

Proceedings of Meetings (Poster Presentations):

Rollins S, Prayson RA, McMahon JT, Cohen BH. Diagnostic Yield of Muscle Biopsy in Patients With Clinical Evidence of Mitochondrial Cytopathy. 90th United States and Canadian Academy of Pathology. March 2001. Atlanta, GA.

Rollins SE, Nielsen GP, Hedley-Whyte ET. Light Microscopy, Electron Microscopy, and Mitochondrial Enzyme Function in Muscle Biopsies for Suspected Mitochondrial Cytopathies. 92nd United States and Canadian Academy of Pathology. March 2003. Washington, DC.

Rollins SE, Nielsen GP, Hedley-Whyte ET. Light Microscopy, Electron Microscopy, and Mitochondrial Enzyme Function in Muscle Biopsies for Suspected Mitochondrial Cytopathies. Massachusetts General Hospital Clinical Research Day. June 2003. Boston, MA.

Rollins SE, Young RH, Bell DA. Autoimplants Involving Serous Borderline Tumors of the Ovary: A Clinicopathologic Study of 30 Cases. 93rd United States and Canadian Academy of Pathology. March 2004. Vancouver, BC.

Michaels PJ, **Rollins SE**, Bounds BC, Brugge WR, Pitman MB. Cyst Fluid Analysis and Endoscopic Features Aid in the Preoperative Grading of Intraductal Papillary Mucinous Neoplasms of the Pancreas. 95th United States and Canadian Academy of Pathology. February 2006. Atlanta, GA.

Rollins SE, Clement PB, Young RH. Uterine Tumors Resembling Ovarian Sex Cord Tumors Frequently Have Incorporated Mature Smooth Muscle Imparting a Pseudoinfiltrative Appearance. 96th United States and Canadian Academy of Pathology, March 2007. San Diego, CA.

White SR, Hecht J, **Kane SE**, Fu Y, Cohen DW, Wang HH. Bile duct brush cytology: indeterminate diagnosis is essential. Arch Pathol Lab Med 2009;133:1689.

EXHIBIT B

SARAH E. KANE, M.D.

Board Certified in Anatomic and Clinical Pathology, and Cytopathology

REFERENCES CITED AND OTHER MATERIAL AND DATA CONSIDERED

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